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Editorial

Looking Ahead

THE INAUGURAL issue of THE AMERICAN JOURNAL OF CARDIOLOGY, the official Journal of the American College of Cardiology, represents a great forward step in carrying out two important functions of the College, namely, postgraduate education and providing a forum for the discussion and dissemination of knowledge and ideas in cardiology. The science of cardiology has made tremendous strides in the past two decades. Current advances in basic and clinical research are proceeding at so rapid a rate that publication and widespread dissemination of these advances are often unduly delayed. At the same time it is difficult for an individual to keep abreast of the rapidly growing literature. This applies particularly to the average clinician engaged in practice.

One may properly ask, why another cardiology journal? It is our belief that there is not only room, but a distinct need for a new journal oriented at the clinical level. Such a journal would serve to crystalize and correlate the various advances in basic and clinical research and apply them to the diagnosis and treatment of cardiovascular disease. Therefore, it is our aim to make this new journal a teaching journal, dedicated to practicing clinicians and cardiologists. Greater stress will be put on the clinical approach to cardiology and the clinical application of the newer graphic, biochemical and other laboratory methods responsible for the recent strides in cardiology. We will derive our papers and editorial material from the research worker as well as the experienced clinician. Controversial subjects will be adequately covered and all points of view will be welcomed and presented. We believe that such a policy will serve to stimulate as well as to educate the clinician.

An attempt will be made to cover adequately all phases and subspecialties of cardiology. For this reason the Board of Editorial Consultants has been chosen carefully to include not only outstanding clinicians but also physiologists, pharmacologists, surgeons, roentgenologists, electrocardiographers, and those engaged in the fields of pediatric cardiology, cardiac catheterization, cardiac hemodynamics, experimental medicine, and public health. The Editorial Consultants will guide the Editors in their selection of material and help to keep the scientific standards of the journal at a high level. Many of the presentations will be in the form of symposia and seminars to be arranged and edited by members of the Editorial Board and other authorities in their particular fields. We will also provide comprehensive and provocative reviews of subjects of current interest. In this way the JOURNAL will be an important medium for postgraduate teaching. Already completed or in progress are symposia and reviews on aortic stenosis, mitral insufficiency, the cardiac in industry, ballistocardiography, open heart surgery, atrial septal defect, rheumatic fever, hypertension, coronary artery disease, myocardial infarction, and many other topics.

We have called on eminent cardiologists all over the world to contribute to the first issues of the JOURNAL and the response has been extremely gratifying. The number and caliber of the articles submitted and their wide range of topics

have convinced us of the great and unanimous need for this JOURNAL. We hope that they will set a high standard for future contributors. The Editors will be unbiased in their policy of accepting or rejecting an article submitted for publication. The important guides will be the quality and character of the material rather than the identity of the authors. We wish to encourage contributions from practicing and independent physicians as well as from research workers and those associated with teaching centers.

In addition to original clinical studies each issue of the JOURNAL will contain one or two stimulating articles devoted to advances in the fields of cardiovascular physiology or pharmacology and experimental cardiology. Other special departments include those devoted to Case Reports, Historical Milestones in Cardiology, Diagnostic Shelf, Query and Answer Corner, What's New in Cardiology, Clinical Conferences, Book Reviews, College News, Notes and Announcements.

THE AMERICAN JOURNAL OF CARDIOLOGY is the newest addition to the Yorke Group under whose auspices are published several other outstanding journals in Medicine, Surgery, and Nutrition. The established reputation of this publisher places the "stamp of quality" on our new JOURNAL. With the initiation of this JOURNAL the *Transactions of The American College of Cardiology* are being discontinued.

As your Editor, I have undertaken this challenging task with great humility and awareness of the tremendous difficulties and problems which lie ahead. I am very grateful for the help, advice, and cooperation given to me so generously and wholeheartedly by the Editorial Board and Consultants and by other noted cardiologists throughout the world. I am confident that the JOURNAL will live up to the high standards set up by the Board of Trustees of the College and its Committee on Publications. In so doing, it will make a noteworthy contribution to the progress of cardiology and medical education.

SIMON DACK
Editor-in-Chief

Clinical Studies

Thirty Years' Progress in Cardiological Diagnosis

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I WANT MY first words to convey to you my expression of gratitude for the honor of having been invited to give this talk to the members of the American College of Cardiology. It is also meant to express my deep gratitude for the high distinction bestowed upon me in appointing me as an Honorary Fellow of this College. This appointment is beyond my personal merits and for this reason I am doubly indebted. When such a distinction as this is awarded for other than mere formality and it is accepted with humility, it establishes between him who gives it and him who receives it a current of noble intellectual esteem which propitiates the strengthening of bonds of friendship.

Tonight's talk is not without difficulties for me. It is neither simple to find the subject nor the way to keep the attention of such a select audience. That is why it was with pleasure that I accepted Dr. Luisada's suggestion one day in Mexico, when we reminisced on our first studies in cardiology in Paris, back in 1926, with the most brilliant representative of French cardiology of his time, Professor Vaquez. Vaquez was the most authoritative figure of clinical cardiology not only in France but in all of Europe. He was to the field of clinical cardiology what Lewis was in laboratory investigation. Luisada left for Italy; I spent another year with Laubry, the brilliant follower of Vaquez, and upon my return I started the teaching of cardiology in my country, precisely in 1927. These memories which took us 30 years into the past suddenly brought up Doctor Luisada's question: "Why don't you talk to us of cardiology as it was practised and compare it with cardiology today. You who have witnessed the changes could tell us how much we have advanced." Then he kindly added: "You are young enough to have kept up to date" and I replied with a smile: "Kind way of saying I am old enough to be able to tell about the beginning of this transformation."

I accepted the assignment gladly. There was another good reason to do so. Since a Mexican physician becomes today a member of this organization, there is no better occasion to say a little of the work done in his country by several investigators. Therefore, with a purely informative purpose, without any intention of overestimating our work or comparing it with that of others, I hope I will be permitted to outline the international aspect and to talk at the same time of the modest contribution of Mexican Cardiology.

The transformation of these last 30 years has been impressive, but this is not because new continents have been discovered in the world of cardiology; it is because the old ones have been filled and changed. There are, to be true, new lands previously unknown, but they are not the best nor the greatest yet. This is because

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in Medicine as is true of science, it is not easy to integrate doctrines which can be called totally an advancement of our day. New things do not spring from nowhere. Behind every great discovery there is always a long list of pioneers who cleared the path. That is why the sage who announces a new conquest is almost never the first. He is often the last in a long list of those who have worked on a theory, that of the pioneers, whose fragmentary work, scattered and incoordinated, culminates after long years in a systematized study, in the integrated vision or in the synthetic conception of him whom we call the discoverer, truly a scientific creator.

It follows that the new things that we take pride in and that I will review tonight are not totally new. Almost all had begun before 1927; in any case, they all have their bases in previous studies.

I find two fundamental factors that account for the extraordinary development, seemingly vertiginous, of the last thirty years. I leave aside, of course, what constitutes the cause itself, the essential reason for any advancement, which is man's talent and his need for knowledge; they account for his interest for observation and his creative imagination.

The first of the important factors of advancement is the *advent of physical, chemical, and biologic sciences to the field of medicine.* Not the timid approach of older days; not the occasional contact, but the massive invasion; the conquest by right. Biophysics and biochemistry have possessed themselves of contemporary medicine and have made us realize that physiologic phenomena are mechanic, electric or metabolic; this means, in the end, biochemical. Perhaps only genetic factors, still so obscure, may escape this simplification. Due to this invasion of natural sciences we have been able to look into disease as into a new world but above all, with new eyes.

This introduction of science, particularly physics and chemistry, has benefited us doctors with a formidable progress in technic. For each phenomenon to be studied a registration or measuring device is invented. From Loewenhock's microscope and Laennec's rudimentary stethoscope to the present cathode ray oscillographs and cineradiography equipment, apparatus has been in the hands of men one of the greatest instruments of progress.

The second factor of progress in our field has been *the advent of cardiology into the field of specialties.* Formerly confused with the vast field of general practice or at least with internal medicine, it has evolved in the last few years as a discipline in the field of doctrine and as a specialty in the professional field. This has permitted clinicians and investigators to dedicate themselves to a circumscribed field of knowledge and has made them gain in depth what they have sacrificed in extension. Thus, pure investigation and applied investigation have flourished. A necessary development has arisen, the need for team work. The analysis of phenomena has reached unsuspected detail. Such is the second of the great reasons for our present progress.

Let us first review the advances reached through the improvement of exploratory technics. We will next go into clinical advancement, which in the words of Sénac has been reached through "chaste observation."

Diagnostic Advances Accomplished by Electrocardiography

In the days when I studied cardiology, this method was already under progress. Before 1927 it had already completed a great cycle from Einthoven and his triangle theory to Lewis with his measurements of activation of the heart. The chapter on arrhythmias was already written in its fundamental aspects. The wonderful book of the English investigator *The Mechanism and Graphic Registration of the Heart Beat* published in 1925 was for us like a Bible.

However, the method ended here, at least as far as its daily practical application was concerned. We, in other fields, saw it as a theoretic method, as something distant from medicine, as a mixture of precision and fantasy. The only practical knowledge derived from it was the identification of arrhythmias and auriculo-ventricular block as well as bundle branch blocks. Such terms as preponderance were used to be sure, such as right and left preponderance. Due to the experimental work of Smith and his monophasic wave in 1916 and

the studies of Pardee on the coronary wave (1920) one could suspect the importance the method would have to express myocardial fiber damage through changes in the shape of the complexes. Perhaps this is why the pattern of heart failure was eagerly sought without avail and the French authors even tried to write a chapter on the subject which they called "Prognostic Electrocardiogram."

Starting in 1927, where Lewis left off, electrocardiography began a second cycle, more fruitful than the first. To the initial studies of Pardee on the pattern of *coronary occlusion*, a new paper was added which remains a classic, by Parkinson and Bedford in 1928, wherein, on the basis of T wave inversion, the first topographic classification of myocardial infarcts is proposed. Pardee completed the pattern describing the large Q wave in 1930. Soon after, Wilson confirmed these findings and offered the explanation of them by changes produced in a dead zone (1933). His experimental studies showed that septal infarction can be diagnosed (1934) and also *myocardial infarction complicated by bundle branch block* (1945).

At this point, the electric pattern of myocardial infarct was well known, but the diagnosis of localization gained another element when Wilson introduced the unipolar leads and fixed with precision through the use of the precordial electrode, the site and extension of the damage: anteroseptal, apical, anterolateral. Dressler first, and later Sodi and his school, perfected the diagnosis of septal infarct and infarction complicated by bundle branch block, correlating the usual pattern with that obtained through the use of an exploring electrode placed at the surface of the septum (1952).

The diagnosis of *angina pectoris* was likewise facilitated with the use of electrocardiography. Feil and Segall recorded the changes of the tracing, particularly those of the T wave, during the course of anginal pain (1928) and soon after, Scherf described the typical negative S-T segment depression, characteristic of subendocardial injury (1939). The short duration of these patterns made it desirable to record the effect of poor coronary blood supply at times other than during the paroxysmal pain. Rothschild and Kissin introduced the hypoxia test (1933) which became practical when Levy set the technic and gave the criteria for calling it positive (1938 to 1946). Since the method was not without difficulties and risks, Master suggested the effort test and established its diagnostic value based primarily on S-T and T alterations (1950 to 1953).

With these advances the electrocardiogram of *coronary insufficiency* was identified in its different degrees and types: ischemia, injury, and dead or electrically inactive zones.

The greatest advance of electrocardiography during this second cycle is due to the introduction of multiple precordial leads of Wilson and his central terminal. In a remarkable series of papers from 1932 to 1944, Wilson reviewed all the problems of electrocardiography. He applied to clinical electrocardiography the studies of ventricular activation carried out previously by Sir Thomas Lewis (later wonderfully studied by Sodi-Pallares) and correlated his experimental findings using direct epicardial leads with the findings employing one precordial electrode and a distant electrode. That is why Wolferth said that "If the hypothesis of Einthoven's triangle is true, the findings of Wilson accomplish the last objective of clinical electrocardiography, that is, the possibility of recording with unipolar leads from the body surface."

This new method permitted Wilson to measure the time of the intrinsicoid deflection and apply it to the diagnosis of *ventricular hypertrophies.*

The importance of this chapter was completed with the study of *ventricular overloadings.* Beyond the unitary idea of Starling (1940) who did not differentiate the pressure overloadings during systole from the volume overloadings during diastole, Cabrera revived the dualist conception (1950) and described different patterns for systolic overloading and diastolic overloading, right and left (1952). Donzelot and his collaborators almost at the same time arrived at similar conclusions admitting adaptation overloadings of the barrier type and volume type (1952). The pattern described by Cabrera as systolic overloading consists essentially of a negativity of repolarization waves at the level of the ventricle involved. In the case of the

right ventricle, in addition, the R wave becomes larger than the S wave in V_1. Diastolic overloading of the right ventricle gives incomplete right bundle branch block patterns and that of the left ventricle elevates and peaks the T waves.

The study of *cardiac arrhythmias* is enriched with the description of a new disorder, characterized by morphologic as well as rhythm alterations. This is the Wolff-Parkinson-White syndrome (1930), the mechanism of which is still obscure despite valuable studies such as Wolferth's (1933), Seger's (1947), Sodi's (1948–55) and Prinzmetal's (1952).

Chronic cor pulmonale may be diagnosed by the electrocardiogram. The changes in morphology and the axis of the so-called pulmonary P wave and the signs of enlargement, overloading and rotation of the right ventricle constitute a valuable pattern for the diagnosis. Kossman (1935), the school of Sodi (1945–46–48) and Goldberger have been among the most important contributors to the clearing of the problem.

Acute cor pulmonale has been identified through the electrocardiogram due to the classic description of McGinn and White (1935) who described the S_1Q_3 pattern, the S-T displacements and positive T waves in lead 1 and negative T waves in lead 3. The explanation of this overloading pattern was first given by Durant (1947) and later by Zuckermann (1950), through a series of experimental correlations. Zuckermann completed in Mexico the series of patterns describing that of *subacute cor pulmonale* in which the dominant element corresponds to T wave alterations.

Mitral valve lesions have their electrocardiographic pattern also. The Argentinean school with Castex and Battro made the first study of the P wave in cases of stenosis (1932). The changes resulting from mitral commissurotomy were simultaneously analyzed by Campbell in England, Puddu in Italy and Soulié in France (1952). The pattern is now totally known.

With my collaborators, Vaquero and Mendoza, I correlated the electrocardiogram with the clinical, anatomic and hemodynamic findings of mitral stenosis. We found that the pattern is completed with three fundamental changes in the QRS complex: change of axis, which rotates more to the right as pulmonary hypertension increases; changes in the R wave, which increases in height in lead V_1 proportionately to the systolic overloading of the right ventricle, and persistence of the S wave, so much deeper in the left precordial leads the more the right heart is dilated and rotated. In the sum of these three factors lies the expression of the degree of narrowing of the valve and the degree of right overloading (1955).

The Mexican school has fruitfully approached the problem of patterns in other valvular diseases. Aceves and Carral (1947) described the pattern of *mitral-tricuspid lesions*, further enriched by the discovery of Sodi of a deep Q wave in V_1, commonly seen in great dilatations of the right auricle.

The pattern of luetic *aortic regurgitation* was pointed out by Friedlander and Reid (1931) and considered nonspecific; it advanced somewhat with the description of Ashman (1944) of initial slurring of the R wave and wide Q_3 and was later made more precise with the study of Friedland and Sodi in Mexico (1949) who interpreted it as incomplete left bundle branch block and completed it with hypertrophy and left ventricular overloading data. This has permitted a singular diagnosis: the distinction of rheumatic and luetic aortic regurgitation, the latter showing the changes described, possibly due to descending myocarditis of the septum (Costero).

Congenital malformations have been among the most benefited with the advances of electrocardiography. The first important contribution was that of Katz and Wachtel who described the large diphasic QRS complexes in a good many of these malformations (1937).

In *atrial septal defects*, Routier and Brumlik pointed out in France right bundle branch block (1940). In a series of papers Vizcaino and Vaquero show its great incidence of up to 90 per cent (1949); Cabrera and Monroy define its hemodynamic significance (1952) and Limon and collaborators studied this malformation exhaustively from the clinical, hemodynamic and electrocardiographic point of view (1953).

Patent ductus arteriosus was formerly considered as incapable of giving any characteristic

pattern, until Cabrera and his collaborators studied it in a series of papers (1950–52) and pointed out the pattern of diastolic overloading of the left ventricle, which disappears after operation and transiently undergoes a stage of systolic overloading. On my part, with Espino, Limón and Dorbecker, I correlated the electric picture with the clinical, radiologic and hemodynamic data and concluded that in patent ductus there is no single pattern, but rather a changing one, according to the stage of the disease, dependent upon the degree of left ventricular hypertrophy, of pulmonary hypertension complicating the malformation and of overloading first of the left ventricle and later of the right one. The pattern would therefore be a faithful reflection, in the majority of the cases, of the hemodynamic situation and a good indication of the urgency for operation (1953).

The electrocardiogram of *pulmonic stenosis* was described by Marquis (1951) and interpreted in the light of hemodynamic findings by Orme (1952) who found a close relationship between the voltage of R and ventricular pressure and by Campbell (1954) who saw in the behavior of the T wave the degree of severity of stenosis.

The electrocardiographic pattern of *tetralogy of Fallot* was studied extensively by Donzelot and his co-workers (1951). *Ebstein's disease* is known in its electric alterations since the studies of Yater and Shapiro (1939) and its diagnosis has become highly probable with the use of intracavity leads by Sodi and co-workers(1955), obtaining ventricular patterns above the tricuspid valve.

Tricuspid atresia can be identified through the finding of Taussig (1936) of the apparently paradoxic left axis deviation (foreseen by Laubry and Pezzi in 1921).

In *aortic coarctation*, classically described as deprived of an electric pattern, I pointed out with my co-workers the usual pattern of left ventricular hypertrophy, commonly without left axis deviation and with signs of left auricular enlargement or damage.

Electrocardiography, which admirably allows the analysis of the electric potential with relation to time, has been complemented by a registration method recording spatial phenomena: *vectorcardiography*. Developed by Mann by the use of a galvanometer (1938) and by Shelong with a cathode ray tube (1937) the spatial tracing was registered by Wilson and Johnston in Einthoven's triangle and designated with the name of vectorcardiogram (1938). Later, Sulzer and Duchosal made an orthagonal registration (1942).

Vectrocardiography has been up to now a complementary method of electrocardiography; a precious means for teaching purposes, merely starting to give its contribution in the field of diagnosis of myocardial infarction, of ventricular hypertrophies and intraventricular conduction disorders.

From the above mentioned, the magnificent path followed by electrocardiography becomes apparent, surely the most fruitful instrument of examination of the last 30 years. No method has renovated itself and progressed so much both as a scientific doctrine and as an applied method which gives excellent information in almost every field of cardiology. From a clinical method, almost always interpreted empirically, electrocardiography became a physical and experimental procedure governed by scientific criteria. Wilson was the greatest worker in this transformation. That is why it can be justly said that we practice Wilsonian electrocardiography and it is certain that anyone who practices it, follows in one way or another his principles and his interpretations.

Diagnostic Advances Accomplished with Phonocardiography

The method is certainly old. The first recordings of the cardiac sounds were done by Einthoven in 1894 with the aid of the capillary electrometer and improved by himself in 1917 with the use of the electrocardiograph. Before 1927 the direct recordings had also been considerably perfected as obtained with the segmented capsule of Frank (1904), improved by Wiggers and Dean (1917). But neither electric magnifying nor the direct method afforded information which could be considered strictly comparable to data derived by auscultation. Yet, it was with these procedures that splendid results were obtained, among which those of

Wolferth and Margolies in the United States (1933) and Lian in France (1935) are outstanding and very specially those of the Argentinian school with Orias and Braun-Menéndez (1937).

Great technical advances came later. Mannheimer, in Sweden introduced the recording by means of frequency bands which he named "calibrated phonocardiography" (1940). This type of recording is excellent but the instrumental set-up is bulky and the technic quite complicated. Rappaport and Sprague in the United States introduced their three types of recording: linear, stethoscopic and logarithmic (1941). Their method is successful, especially because it records sounds exactly like those picked up by the clinician's stethoscope. Maas and Weber in Germany record by means of frequency bands capable of being inscribed directly (1952) and Luisada in the United States was able to record "selective phonocardiography" wherein the recordings of Rappaport and Sprague are complemented with the selection of frequency bands (1956). Lastly, Lewis accomplished the most recent technical perfection with intracavity phonocardiography (1957).

Phonocardiography has permitted the distinction of the different types of gallop rhythms described by Wolferth and Margolies (1933); the identification of pleuro-pericardial snaps recorded by Lian (1935) and, clinically described by Gallavardin since 1913; the recognition of pericardial calcification revealed by the protodiastolic vibration described by Lian (1941); the opening snap of tricuspid stenosis described by Rivero Carvallo (1950) and especially a very important contribution which ordinarily escapes the ear, the measurement of the delays of the inscription of the first sound in mitral stenosis, successively studied by Luisada (1941) and Cossio and Berconsky (1948) during fibrillation and later by Wells (1952) and by Fishleder (1954) during sinus rhythm. These studies have clarified the fact that delays are much larger as the stenosis becomes more marked. Of considerable interest has been the study of Fishleder and Medrano on the relationship between the two intervals, the one between the Q wave and the first sound and the one separating the 2nd sound from the opening snap, to evaluate the degree of mitral stenosis (1956).

It goes without saying that phonocardiography has recorded all types of precordial acoustic phenomena: sounds, murmurs, rubs, snaps. The tremendous amount of physics and electronics and the perfection reached in recordings have given precision to many obscure points of auscultation and have helped to clarify the mechanism of production of the sounds. The physiology of sounds and murmurs and clinical teaching methods have been greatly benefited by them. Clinical diagnosis has gained less. It has been benefited inasmuch as our information derived thereof has been refined and perfected in regard to auscultation without adding many new things. That is why auscultation continues to be, when practised by trained ears, one of the most solid pillars of cardiologic diagnosis.

Diagnostic Advances Due to Radiology

Fluoroscopy, teleradiography and orthodiagraphy were currently used before 1927. The radiologic method seemed exhausted at least in its essential contributions. Vaquez and Bordet had written in their book "*Radiologie du coeur et des vaisseaux de la base*" all that we knew on the subject. Chaperon introduced however, a new element, with postmortem opacification of the heart and great vessels in order to establish the topography of the heart chambers and interpret the semiology of the pulmonary hilar vessels (1925). Heim de Balsac extended the method and on the basis of those studies a clinico-radiologic correlation was possible which was published two years later in France by Laubry, Cottenot, Routier and Heim de Balsac, where the classic radiology of the heart is summarized (1939).

But in the last 30 years radiology has undergone a splendid transformation. In 1930 *tomography* was discovered in Italy with the studies of Vallebona, who was able to dissociate radiologic images through sections at different depths. Soon after, Zeider des Plantes in Holland independently described a similar procedure in 1933 which he called *planigraphy*. During many years the method did not seem to progress due to medical skepticism but to-

day it has proved its great value. Large pulmonary lesions not visible in ordinary radiograms, such as tumors, infarcts or cavities, are clearly seen with tomograms. In our field, it gives valuable information: aortic coarctation is seen in detail very much like in an angiocardiogram; pericardial or valvular calcifications which escape ordinary methods are identified with tomography; also, an extravascular tumor is differentiated from an aneurysm.

Fluoroscopy itself has been wonderfully renovated. Helen Taussig has shown the great value of cardiac dynamics in the recognition of congenital malformations. Sosman, Heim de Balsac, Dorbecker agree on the value of this indispensable complement, which allows dynamic visualization of the radiologic shadow. This did not escape older generations and precursors are to be found here too. Deneke, in the beginning of the century had pointed out that in Roger's disease there is great amplitude of the heart beat for both ventricles. De la Camp and Bittorf had found that in patent ductus arteriosus the pulmonary segment has a large pulsation which is synchronous with ventricular systole.

Other excellent examples of the value of the method are those of the to and fro movement of the entire left border of the heart in patent ductus arteriosus in contrast with the meager beat of the right border; the systolic beat of the left auricle in mitral regurgitation; the quietness of the cardiac shadow in Pick's disease and the infinite variety of combinations in congenital heart disease according to the type and its hemodynamic behavior.

Registration of chronology and amplitude of the beats has been done with *roentgenkymography* of Stumpf in Germany (1927) and that of Cignolini in Italy (1931). Stumpf's method was not very sensitive and it was modified in the United States by Chamberlain and Boone through the introduction of a photoelectric cell which records the changes in density of the shadow (1945). The method gained in sensitivity but it became laborious and difficult to obtain pure curves due to the registration of many parasitic curves.

Analytic kymography of Cignolini is both sensitive and practical; it allows the selection of the fields and the magnification desired for the study of cardiac dynamics. It is a good exploratory instrument.

The most spectacular improvement of contemporary radiology was the advent of *angiocardiography*. The credit of the precursors belongs to Pérez Ara (1931) and the Portuguese authors, Carvalho, Egaz Monis and Saldaña (1934), who were able to visualize the opaque substance within the pulmonary vascular network. But angiocardiography was really born in 1937 in Cuba, when Castellanos established the technic to opacify in living subjects the right chambers of the heart as well as the pulmonary vessels. This modification, with the aid of penetrated technics, allowed him to study a certain number of congenital malformations. One year later, Robb and Steinberg in the United States applied Castellanos' method to adults and they established the bases for a new technic, taking into consideration the circulation time of the blood (1938). In Mexico another step was taken when I introduced with Dorbecker and Celis the opaque substance directly into the right cardiac chambers by means of an intracardiac catheter (1946). Dilution of the contrast medium was thus reduced considerably; the image gained in precision and above all, the injection may be made exactly at the site where examination is most needed: auricle, inflow tract, outflow tract of the right ventricle, etc. Thus came into being the so-called *selective angiocardiography*, so designated by Johnson of Sweden who perfected the technic in 1950. The Swedish school has contributed with great progress. Wegelius devised a machine with an electrocardiograph introduced in the firing mechanism which tells the operator whether the picture was registered during systole or during diastole and to discard the false images of stenosis (1952). Instead of the short number of plates which we ordinarily use, Schönlander has increased them to 20 per second with his new seriograph; these plates are equally distributed in two perpendicular angles. The large number of images allows a finer analysis and a better correlation with the dynamic concept. Angiocardiography has been a fruitful advance,

especially in congenital heart disease. The passage of opaque substances from one auricle or ventricle to the other has been visualized in atrial and ventricular septal defects; aortic overriding in tetralogy of Fallot is visible with the simultaneous filling of the right ventricle and the aorta; aortopulmonary fistula is visualized through early filling of the aorta and patent ductus arteriosus may be discovered through prolonged filling of the pulmonary artery or its "two step opacification" as we called it. The method has likewise permitted us to differentiate with precision the aneurysms from the tumors which simulate them; interior opacification dispels all doubts.

Angiocardiography constitutes a method of dynamic radiology. Images are interpreted in the light of the shape and the size of the cavity or vessel opacified and taking into consideration the time at which the image appears, a fact that permits us to know whether there is an obstacle to the current as in pulmonary stenosis or if on the contrary there is an abnormal passage between both circuits.

Aortography came later, as a complement of angiocardiography. Dos Santos opacified the abdominal aorta (1937); Meneses Hoyos and Gomez del Campo, the thoracic aorta by direct aortic puncture (1946). Radner did it by retrograde filling, introducing a catheter through the brachial artery (1948). Arteries tolerate less dye than the veins and these methods are not entirely without risk; yet, this is smaller than would be thought at first and images are very neat and clear. With this method aortic coarctation and patent ductus arteriosus may be studied with detail preoperatively in order to decide on the operative procedure.

The study of the *peripheral vascular system* has included that of the cerebral network, the merit of which must go to Egaz Monis (1934). The lower extremities have also been studied either from the venous or from the arterial point of view.

The last step in cardiovascular radiology of our days has been to complete angiocardiography with *cineradiography*. Instead of a few plates per second, higher speed, that of moving pictures is obtained: 16 to 72 frames per second. The precursor of this innovation was Janker in Germany, who was able in 1940, with the use of very luminous lenses, to obtain wonderful images. Today with electronic advances one may use an intensifier whose luminosity is 500 times greater than that of ordinary fluorescent screens. Photography with a movie camera takes care of the rest. The first tests have been done in Mexico with Phillips equipment. Dorbecker studied 20 patients with it which allowed him to visualize the passage of the opaque substance; subsequently a careful analysis of the picture was possible in detail.

Advances Through Ballistocardiography

A method has appeared in the last few years with the rare virtue of arousing the interest of a large number of investigators and promoting the skepticism of many: ballistocardiography. It had two great pioneers: J. W. Gordon, who described the mass movements registered in the human body by the effect of circulation (1877) and Henderson, who further developed the study of these movements demonstrated by a retrocess curve (1905).

Actually, present ballistocardiography started with the studies of Starr, Rawson, Schroeder, and Joseph (1939). The procedure seeks the registration of the body movements produced by cardiovascular activity. It studies the action of the heart as a bomb as the latter determines retropulsion movement of the body produced by systolic activity and the impact of the blood in the heart chambers and the great vessels. This group of forces, acting in an opposite direction, causes a series of movements of the body which are recorded as curves; some would be related to the force of cardiac output, others to the impact of the blood on the valvular and vascular barriers and others to the slowing of the blood column.

The recording of the BCG was possible with the high frequency table developed by Starr *et al.* (1939) which was none other, in its beginnings, than the suspended table of Henderson. This first device has undergone numerous modifications, either to absorb the movement and render the table aperiodic (Deuchar, Talbot and Scarborough, 1955) or to record movements in different positions (Witter and Reissmann, 1948), or to record directly from the

body (Dock and Taubman, 1949). The latter has been the most important modification to make the method useful in clinics. To it has been added the photoelectric registration when the main interest is in movement or else the electromagnetic registration when the desired information is velocity.

It is beyond question that the BCG can supply useful information, but it is still in its beginnings. The curves are so polymorphous that it is not always easy to decide when they are normal and when pathologic. There is a large number of factors which deform them such as respiration, digestion, effort, emotion, tobacco and especially age, to the point that the tracing is practically always normal in young people, abnormal in 45 per cent of subjects over 50 years of age and definitely abnormal in 94 per cent of people in their eighties (Scarborough, 1953).

The main contributions to diagnosis have been in the field of coronary insufficiency, angina pectoris, and myocardial infarct. In those who suffer angina pectoris the BCG is almost always abnormal, even though the electrocardiogram is not decisive (Dock and Mandelbaum, 1951; Soldati, 1953). It is the effect of the changes suffered by the contractile force of the myocardium and thence its importance for prognosis. Some authors even go so far as to say that in cases of coronary heart disease the BCG has a higher diagnostic value than the electrocardiogram (Smith *et al.* 1955) and that in cases of infarction, the course towards improvement is better followed with the BCG than with the electrocardiogram (Mendelbaum and Mendelbaum, 1953).

In arterial hypertension, valvular heart disease, heart failure and all types of myocarditis, BCG alterations have been described which are useful for diagnosis. Actually, there is no chapter in cardiology where the BCG has not been applied. It is of interest, however, to point out the vague nonspecific and not always demonstrable nature of the greater part of these changes. Due to the fact that there are many variable factors, some dependent upon the cardiovascular system and some on the different body tissues and because beyond a certain age all the tracings are abnormal, it is difficult not to be skeptical about the changes of BCG. The outcome of these doubts is a contradictory situation: while for some the BCG is a unique method to estimate cardiac strength (Starr, 1954) and the best way to estimate the systolic activity of both ventricles and the changes in velocity of their emptying period (Dock, 1953); for another important number of cardiologists the method is still quite uncertain and must become perfected before it is introduced in daily practice.

Diagnostic Advances with Cardiac Catheterization

Cardiac catheterization is one of the new lands in the world of Cardiology. The method did not exist before 1927 except in physiologic laboratories. Its daring precursor was Forssmann in Germany, who introduced a catheter in one of his own veins and reached the right heart chambers (1929). Catheterization as a scientific procedure was truly born in the United States in 1941 with Cournand and Richards. In a wonderful series of papers (1941 to 1949), Cournand, Richards and their coworkers set the technic, registered pressures in the different segments of the right heart, studied gas analysis, measured the cardiac output with the aid of Fick's principle and explored the field of congenital heart disease. The pulmonary circuit was studied in all its aspects and its pressures and its resistances measured by McMichael (1944), Dexter (1946) and Bing (1947) and by Lenègre (1949). These became the bases for outlining hypertensive pulmonary syndromes, both primary and secondary to heart or lung disease. Capillary or precapillary pressure was measured by Dexter and Hellems (1949) and by Werkö and Lagerloff (1949). With it the best explanation for acute pulmonary edema is offered. Brannon, Warren and Weens were the first to study hemodynamics in atrial septal defect (1945). Patent ductus arteriosus was studied by catheterization in Sweden by Götsche, Handon and Eskildsen, at the same time that it was done by Rubio and Limón in Mexico, who later did it routinely (1948). Not only is a diagnosis confirmed with this method but the atypical cases complicated by pulmonary hypertension can be identified, as shown

by the Mexican workers (1948–53) and by Souliè and Bouchard in France (1951).

Zimmermann first (1950) and soon after Limón and co-workers catheterized the left heart chamber in man (1950) by retrograde catheterization of the brachial artery, which incidentally permitted Sodi-Pallares to study for the first time the intracavity potential of the left ventricle (1950). That of the right cavities had already been recorded by Lenègre in 1946. Cournand and Lecquime studied the pulmonary circulation in heart failure (1951) and Taquini further investigated with catheterization the field of chronic lung disease (1950); the result of both works is the setting of boundaries separating circulatory disturbances in one field from another. Nylin was able to perfect the measurement of circulation time with the aid of radioactive marked red blood cells and he determined the presence of residual blood in the ventricles in cases of heart failure (1946). Burchell and Wood, with the aid of dye dilution curves cleared the problem of localization, importance and flow of abnormal communications between the systemic and the pulmonary circuits (1950) and Wood simplified the examination with his method of oximetry using photoelectric cells (1950). Finally, Beato Nunez and Ponsdomenech in Cuba and Björck in Sweden advocated direct puncture of the left ventricle and the left auricle to record their pressure (1953).

With this information, at the time of arrival of cardiac surgery, especially that of mitral stenosis, the method is capable of giving all sorts of data, from the amount of hypertension within the pulmonary artery which accounts for right ventricular overloading, to the pressure in the capillary circuit, which gives rise, when it becomes elevated, to bouts of acute pulmonary edema; from arteriolar resistances to total pulmonary resistance and from cardiac output to the measurement of the area of the mitral valve with the aid of Gorlin's formula (1951).

Catheterization has been one of the most extraordinary successes of contemporary medicine. It is the introduction of physiology itself with all of its recordings into the cardiac chambers and into both circulations. With the radiologic picture of the catheter one can judge the size of the cavities and of the abnormal paths that the catheter can follow. With intracavity and intravascular pressures one is aware of the degree of overloading suffered by a given portion of the heart; with the samples of blood taken at different levels, the saturation of the blood can be determined and the eventual mixing of arterial and venous blood discovered, and also the direction of the shunt; the application of Fick's method permits us to determine cardiac output; pressure gradients found along the path permit us to discover the obstacles for the free flow of blood and the importance of these obstacles; the type of pressure curves renders information on regurgitation due to tricuspid or mitral insufficiency.

The mass of information given by catheterization is priceless in the diagnosis of congenital heart disease and in several acquired heart diseases. In constrictive pericarditis it shows the extreme reduction of cardiac output and the typical plateau curve with the added vibrations of Hansen. In mitral stenosis it measures the degree of valvular narrowing and its hemodynamic repercussion; in heart failure it measures diastolic hypertension and due to it, the amount of residual blood in the ventricle. In chronic cor pulmonale it measures arteriolar resistances and through them, those of the lesions in the lung. In arteriovenous pulmonary aneurisms it measures the flow through the abnormal anastomoses, etc. None of this could be done before 1927. All of it has been a genuine advance of our time. A long list of investgators from the American and the European continents have obtained priceless information in a few years. Along with specific contributions others of more general scope have been added which contribute to give cardiac catheterization its just value as a diagnostic method. Cournand, Dexter and Bing in the United States; Lenègre, Soulié, Carlotti, Joly and Bouchard in France; Lecquime in Belgium; Maier, Bayer and Loogen in Germany; Mannheimer, Lagerloff and Werko in Sweden; Zak and Holling in England; Limón and Rubio in Mexico, all of them contributed to set the technic and the methodology of the new procedure and to establish the pattern of morphology of pressure curves (1947 to 1950).

Cournand and his co-workers have enriched Cardiology with a physiologic method of the greatest importance. Clinical diagnosis gains as much as does the physiopathologic doctrine. Rarely has a Nobel prize been as well deserved as this. When we contemplate this with genuine pride, one cannot help but meditate with sorrow on the fact that Frank N. Wilson died prematurely without receiving his.

Clinical Advances

With the aid of the above mentioned technics, advances in clinics have been extraordinary. We have mentioned them as we reviewed the different methods. But there are many that have been accomplished following different paths, those of classic clinical methods, those of anatomic correlation and clinical laboratory, and finally those derived from the application of statistics. Many of those advances are related especially to etiology, mechanism of production and treatment. We will put them aside, despite their importance, to limit ourselves exclusively to those which constitute an advance in diagnosis.

RHEUMATIC CARDITIS

Before 1927 valvular lesions were one of the best known chapters. One lesion, however, remained obscure: that of the tricuspid valve. We knew how to identify its regurgitation and we almost invariably diagnosed it as a functional disorder. Its incidence as a necropsy diagnosis was revealed by the studies of Cabot (1926) and the contributions of Herrmann, of Levine (1937) and White (1939). Aceves and Carral correlated the clinical and anatomic findings and called our attention to the great incidence of *tricuspid lesions*, of up to 33 per cent in rheumatic heart disease, capable of giving clinical recognizable signs pre mortem (1947). Rivero Carvallo added an important maneuver, that of post-inspiratory reinforcement of the systolic murmur in tricuspid regurgitation. Although this is not a pathognomonic sign, it is positive in the majority of the cases (1946).

Tricuspid stenosis is possible to diagnose in daily practice. Rivero Carvallo described the opening snap of the tricuspid valve (1950); electrocardiography shows the great incidence of deep Q waves in V_1 pointed out by Sodi (1953); catheterization has added the characteristic pressure data.

Diagnosis of *mitral stenosis* has been perfected to a high degree especially through catheterization. Today, through a close correlation, clinicians are able, without catheterization, to diagnose with great accuracy mitral stenosis, to define the degree of valvular narrowing, the degree of venous capillary pressure and the importance of overloading of the right ventricle. In this re-evaluation of clinical semiology the main contributors have been Lenègre (1951), Soulié (1953), Froment (1953) Lewis (1952) and the workers at the National Institute of Cardiology in Mexico (1954).

Along with rheumatic *aortic stenosis*, long known, we have come to recognize *aortic calcific stenosis*, which has a different clinical picture, be it a complication superimposed on rheumatic lesions as proposed by Christian (1931) and by Karsner and Koletsky (1947) or be it an added complication sometimes of rheumatism, sometimes of atherosclerosis, as originally stated by Mönckeberg (1904) or whether it is seen on rheumatic or syphilitic or congenital lesions (Chávez, 1956). The diagnosis has been perfected, other than through certain clinical signs of relative value, by the visualization of calcification itself by means of x-ray studies, as pointed out by Sosman and Wosika (1933) and by the almost universal presence of left bundle branch block or at times of right bundle branch block, as pointed out by Rodriguez and Sodi-Pallares (1951).

Bland and Jones' contribution has been of great importance; it has shown us that the diagnosis of valvular lesions may take years to prove, sometimes ten and sometimes twenty (1951).

The diagnosis that has advanced more considerably during our time is that of *rheumatic activity*. Before 1927 we based it fundamentally on heart failure, which the French school called inflammatory failure, as well as on blood reaction signs and the general signs which reveal the presence of the infection. Currently, the picture has been enriched with the identification of beta hemolytic streptococcus as a determining agent of rheumatic fever, a fact established

especially by Coburn (1931). Immunologic response to streptococcus, therefore, has been regarded as the test of aggression and as the measure of the organic response. That is why it is so important to determine the level of antistreptolysins in the blood, pointed out by Todd (1932), of antifibrinolysin, pointed out by Tillet (1934), of antihyaluronidase, pointed out by Friou and Wenner (1947) and that of C-reactive protein, also pointed out by Tillet since 1930 and incorporated in clinical work in the last few years. One of these substances, at sufficiently high concentrations, suffices to prove the antigenic agression. Stollermann has proved that in any infection due to hemolytic streptococcus at least one of these substances is elevated and generally all of them are (1956).

Despite these advances, the possibility of doing heart biopsies has proved how far we are from the correct diagnosis of rheumatic activity in our patients with carditis. The removal of the left auricular appendage during mitral commissurotomy has permitted the histologic study of the lesions and we have learned that cases considered as quiescent often hide active lesions not recognizable by the clinician (Björck *et al.* 1952; MacNeely *et al.*, 1953). In 100 biopsies of this type at the National Institute of Cardiology in Mexico, we found 63 per cent of the cases with Aschoff's bodies or with lymphocytic infiltrations characteristic of rheumatic activity, which shows lack of sensitivity of our present methods (Chávez *et al.* 1955).

The advent of antibiotics, particularly penicillin, which eradicates hemolytic streptococcus has changed the course of rheumatic heart disease. We now are able to recognize a cyclic evolution for the germ, which is self-limited from three to six months according to Massel and up to nine months in Mexico according to Mendoza (1956).

Violent rheumatic activity has permitted us to identify new visceral pictures. The old concept of cerebral rheumatism gains support with Brvetzch's description of cerebral obliterating arteritis in some patients who died with rheumatic fever (1944). However, diagnostic progress came when De Gortari, Pellón and Costero described at the Institute of Cardiology in Mexico, *rheumatic encephalopathy* leading to delirium or coma. Its course is always fatal and its anatomic lesions are apparently specific, including the presence of characteristic nodules springing from neuroglia, similar to Aschoff bodies in the connective tissue (1952). *Rheumatic pneumonitis* has also been identified clinically and radiologically and it has been found to be more common than ordinarily realized, up to 11 per cent during rheumatic carditis (Griffith *et al.* 1946). Cuéllar has shown how often it is mistaken for other acute and subacute pulmonary diseases and how it may be identified in view of its rich and changing pulmonary signs, corresponding with the radiologic picture (1951).

Therefore, clinically the diagnosis of rheumatic carditis has advanced importantly; but the major progress has taken place in other fields: those of etiology, immunology and prevention.

CORONARY HEART DISEASE

The greatest advance, the most fruitful clinically in the last 30 years, has been the diagnosis of *myocardial infarction* and its allied picture of *coronary insufficiency*. It is true that clinical recognition had been accomplished long ago by the precursors Hammer, Huber and Leyden in Germany at the end of the 19th Century; by Obrastzow and Straschesko in 1910 and especially by the fundamental work of Herrick in 1912 and 1917. But the medical profession was not identified with the doctrine and did not currently make the diagnosis until the last 30 years.

In contrast with this delay, no other disease has been more studied and no other has received so much attention as this. In its clinical study all the schools of the world have contributed. To myocardial infarction are attached the names of Parkinson and Bedford in England, Gallavardin and Laubry in France, Barnes and Whitten, Wolferth, Wood, White and Levine, Wright, Levy and Master in the United States, Nylin in Sweden and many others in other countries. The list of clinicians could be interminable and there would still be a great list of electrocardiologists, because no source of information is more valuable to establish the diagnosis and limit its borders as electrocardiography. This has been the great instrument of work which together with

anatomic findings has permitted clinicians to identify all the forms of infarction, both painful and silent, those that occur with syncope and those that lead to dyspnea; it has permitted them to locate the infarcted area at septum and in the free wall; subepicardial, subendocardial and transmural; clinicians can recognize all the types and all the degrees, to the point where this disease, which hid away from physicians mysteriously for centuries is today the easiest and surest to diagnosis in the majority of the cases.

There is one anatomic study of particular interest in the understanding of the different forms of coronary involvement: that of Blumgart and Schlessinger. This study has emphasized the value of anastomotic circulation between the large coronary arteries and which accounts for the tolerance or intolerance of the heart to the occlusion of one of them (1937–40). In the last few years one study promises a great advance in the diagnosis of infarctions: that of glutamic transaminase, a method advocated by LaDue to recognize the presence of a myocardial necrotic area with sufficient specificity to avoid confusion with necrosis of other organs (1954–56).

ARTERIAL HYPERTENSION

Recent advances in the diagnosis of arterial hypertension have been important although not spectacular. Hines and Brown described a test based on the reaction to cold and discovered a lot of hyperreactors (1933); it is still to be seen if these are the future hypertensives. Keith, Wagener and Barker undertook the first systematized study of the retinal circulation and described its four degrees: on the bases of these, they proposed the first prognostic classification of hypertension (1939). Although its validity has been questioned because of its restricted field and dogmatism, it is nonetheless true that it contains a great amount of truth which is a useful guide in clinics. *Malignant hypertension* appears in clinics. It was foreseen by Fahr, who even described its anatomic bases made up of necrosis of the renal arterioles (1914), and afterwards by Volhard as a final stage of nephrosclerosis (1917). It was recognized not as a specific disease but as a final stage of any type of hypertension. The description of the characteristic clinical picture is to be attributed fundamentally to the Anglo-Saxon school with Keith, Allen, Fishberg, Pickering, Perera and Goldring (1928 to 1945).

The diagnosis of *paroxysmal hypertension* due to pheochromocytoma is also an advance of the last thirty years. It is true that the first case was described a few years before by Labbé (1922); but it was after 1927 when the clinical picture was described with precision. Roth and Kvale introduced the diagnostic test with histamine (1945). Afterwards came those of benzodioxane (Goldenberg 1948), regitine and others. The greatest advance was the introduction of microchemical methods to discover the catecholamines discharged in the urine and blood of these patients, an advance due to Lund (1949) and Von Euler (1951). We are now able to recognize permanent hypertension in a good half of these patients with pheochromocytoma due to Goldenberg's studies (1952). We are also able to recognize the Cushing type of hypertensives in certain disorders of the hypophysis and suprarenal cortex. Finally, the discovery of aldosterone (1953) has permitted Conn to describe primary aldosteronism as a frequent cause of arterial hypertension. Thus, a chapter of hypertension of endocrine nature has been completed as opposed to the well known hypertension of renal nature. The spendid experimental studies of Goldblatt (1932) and those of Houssay and his school (1932) and those of Page (1932) on ischemic kidney permitted us to delve into the physiologic mechanisms of hypertension, but as yet have not received a parallel important clinical advance, nor have they solved the problem of essential hypertension. The interesting and important studies of Raab (1944-56) and of Page (1950–56) on the neurohormonal mechanisms of hypertension, except in a few cases of so called surgical kidney, still await proven implications in the field of diagnosis.

VASCULAR DISEASE

The syndromes of arterial occlusion have been extended and detailed in many points. Lériche described the picture of thrombosis with slow obstruction of the abdominal aorta (1940). This picture is subject to surgical treatment.

Atherosclerosis in itself, as a biologic process has greatly advanced as regards its mechanism

of production, and is still beyond our diagnostic possibilities in its early stages. In order to recognize its important localizations we must await its expression through circulatory insufficiency in the coronary territory, in the brain, in the retina, in the kidney or at least in the lower extremities. We are still awaiting a test which will allow us to recognize atherosclerosis in its beginnings. We cannot say that we have not advanced, because the electrocardiogram, the examination of the eye grounds, the kidney function tests, oscillometry and plethysmography of the lower extremities often permit us to identify its presence before the appearance of important symptomatology.

CONGENITAL MALFORMATIONS

Conversely, in the diagnosis of congenital malformations of the heart the advances have been impressive. Those of you who are old enough will remember how limited our knowledge was before 1927. Vaquez accused his contemporaries in 1921 of looking upon these malformations as though they were clinical teratology deprived of interest. The most comprehensive synthesis of those days was the book of Laubry and Pezzi (1921) written to call the attention of cardiologists to this subject, because up to that time, said the authors, it was of interest only to pediatricians and anatomists; the remainder of the medical profession regarded this branch of medicine as if it were "the poor relative whom one prefers to ignore."

The descriptions by Laubry and Pezzi are wonderfully clear, brilliant, and full of sound clinical judgment. Even today one may read them with benefit and sometimes with pleasure, but the field, one must admit, was poor, exceedingly poor. Suffice it to say that at that time patent ductus arteriosus was so seldom diagnosed, that Herxheimer in 1910 was only able to collect 38 cases from the literature and Laubry and Pezzi in the following 11 years added only five more cases. Today, instead, no one could say how many thousands there are. I for one, studied 200 cases at the Institute of Cardiology in 1953.

At that time, we were only beginning. One was reasonably certain of the diagnosis in a case of aortic coarctation, of tetralogy of Fallot, of patent ductus arteriosus, of dextrocardia, sometimes of a septal defect. The rest was an obscure field where one might conjecture and arrive only at a very approximate diagnosis. It is because at that time we lacked all that today renders diagnosis certain. Fluoroscopy, which may be termed selective, was in its baby stage; there was no angiocardiography or kymography; the electrocardiogram only offered the patterns of preponderance, right or left; there was no cardiac catheterization and gas analysis could be no poorer, limiting itself to the method of Plesch.

Starting in 1927, the events follow each other with speed. Precisely in that year, Maude Abbott produced her excellent clinical classification on the basis of 1,000 postmortem cases. This was the beginning of an orderly conception of the subject. Another wonderful woman followed: Helen Taussig, who obtained from the anatomic and clinical method, with the aid of intelligently handled fluoroscopy, a large amount of information. Then came the extraordinary progress of exploratory technics: electrocardiography, angiocardiography and finally, heart catheterization. Along with those technical advances came the progress of clinical semiology clearly interpreted. Outstanding in this subject is the wonderful work of Donzelot, Durand, and their collaborators from the Broussais Hospital (1954).

All of this accounts for the great advances in diagnosis already mentioned. Even the obscure pictures of complex malformations or of atypical forms such as Ebstein's disease, tricuspid atresia and transposition of the great vessels, are now possible to diagnose. A good example is patent ductus arteriosus complicated by pulmonary hypertension which clinicians were unable to identify in view of the atypical picture. Nowadays, the passage of the catheter through the ductus and the registration of high pulmonary pressure are enough to identify it (Limon *et al.* 1950). Correlating all of the information at hand, I described with Espino Vela, Limon and Dorbecker, the specific syndrome of this complicated malformation (1953) already recognizable by clinical means without having to resort to catheterization. Other isolated contributions have been of great aid. Railsback and

Dock described the sign of rib notching, which aids in the diagnosis of coarctation of the aorta (1929).

OTHER TYPES OF HEART DISEASE

Other fields of clinical cardiology have been likewise benefited. We learned of the existence of heart disease due to *vitamin deficiencies*. Wenckebach described that due to beri-beri (1928). *Heart diseases of collagen nature* were also described. This is a chapter where a number of ailments meet with each other, which have in common a disorder in the connective tissue, such as lupus erythematosus, periarteritis nodosa and scleroderma. Friedberg described periarteritis nodosa associated with rheumatic heart disease (1934). Klemperer *et al.* pointed out the presence of L.E. cells which facilitate the diagnosis of lupus erythematosus (1942). Robles Gil pointed out the high incidence, usually unsuspected, with which lupus damages the heart (1948). Pollack described the heart lesions in scleroderma (1940), later confirmed by many workers.

Nonspecific acute myocarditis can be diagnosed clinically with accuracy. To the well-known diphtheritic, typhoid and pneumonic types of myocarditis, others have been added: those produced by spirochetes, the typhic myocarditis, studied by Vaquero (1935), Chagas' disease, well studied by the Brazilian school (Laranja, 1942) and by the Argentinean school. Finally, those due to virus of the most varied nature: poliomyelitis, virus hepatitis, yellow fever and infectious mononucleosis.

Along with these specific contributions is the work of the great semiologists of our time who have reviewed and perfected these contributions, transforming the data supplied by technics to live doctrine. They have contributed as much as investigators themselves in this renovation of which we are proud. From this point of view the work of Laubry, Gallavardin, and Lian, Romberg, Parkinson, Wood, Campbell, and Pickering; White, Levine, Friedberg and Cossio is outstanding.

Conclusion

Thus are briefly summarized the great advances we have accomplished in the last thirty years. It would be useful to insist upon the fact that I have only referred to diagnostic advances and not to all of cardiology. Great and extraordinary progress has taken place in other chapters: in physiology, pathology, etiology, prevention and medical as well as surgical treatment, but these are not the subject of this paper nor have they contributed to our improvement in diagnosis.

My revision is not and cannot be complete and I admit that among the facts that I have pointed out, some may not be the most important. They are in any case those which have seemed to me the most valuable in clinics or most fruitful in their implications. They are, on the other hand, those which I have been able to follow more closely in my 30 years as a teacher of cardiology, seen from my own point of view, in my own environment and in my time.

In this comparative vision between yesterday and today, not only do the differences stand out, but also the path followed is visible and the reason for these changes is apparent. More than 30 years ago, in the first quarter of the century, the best instruments of diagnostic advance were a sound clinical observation and the pathologic corroboration. Today these two methods, without decreasing their value, have been supplemented with physiologic studies. Physiology with all its measures, its recordings, is what has added a dynamic approach to our studies. Electrocardiography, angiocardiography and heart catheterization are none other than applied physiology. What has changed us, therefore, is the concept of things; we think with a functional criterion and not only with a morphologic point of view. Restrictive medicine of the beginning of the century, mainly inspired in the study of lesions, changed its sign, incorporated physiology and with it biochemistry and later, the world of the psyche. Today it tends towards integrated medicine; to the study of cause and effect, functions and lesions, body and spirit. We are headed towards the concept of unity, whence the medical philosophers started in the Greek world.

Does this mean we have reached the goal of integrating our medical studies, that we have truly reached the criterion of unity within the diversity? We are far from it. We have not

reached the goal, but we have at least seen the way. In practice, we continue to debate on partial subjects, with excessive specialization, with unilateral conception of phenomena. We have advanced so much in analysis that we have lost much of our capacity for synthetic conceptions. We have subdivided the field of our patients to such an extent that we often lose sight of man as a whole. And as we become more perfect in our field, at times very small, we have left behind the ideal humanist physician and still farther behind the philosopher physician. To correct this mistake is one of the fundamental goals awaiting us. It is as important as the search for biologic truth itself which we pursue. I would add that that is the answer to the truth.

Some Puzzling Points Concerning Angina Pectoris*

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ANGINA PECTORIS presents an impelling challenge to the medical profession from more than one point of view. Here we have a common condition that generally is easily recognized, in which the pathologic changes can be fairly well predicted and clinical behavior foretold in many respects, yet one that leaves so much about it unanswered. There are few diseases in which the diagnosis can be made so readily from the history alone. In fact, there really is no other way to make the diagnosis. If a patient complains of certain symptoms so graphically described by Heberden in his classic work, he has angina or he is malingering. Discussing the latter possibility, when the history given by the patient is clear and satisfactory, as is often the case, (though there are well known variations in the type of complaints) the diagnosis of angina must be made. Examination of the heart or various tests such as x-ray, electrocardiogram, chemical and functional tests may elicit evidence of other forms of heart disease or of myocardial infarction or of coronary pathology, but will not add to or detract from the diagnosis of angina (except indirectly).

The diagnosis of angina signifies a peculiar state of the heart. Although in the overwhelming majority of instances it connotes atherosclerosis of the coronary arteries, these vessels need not be abnormal. The coronary arteries may be normal in the occasional patient who has anginal distress during paroxysmal rapid heart action with a rate of 200 to 250, in some cases of aortic and less frequently of mitral valvular disease, in a very rare instance of anemia or thyrotoxicosis, and possibly in other conditions. The important point is that if the patient complains of these peculiar constricting sensations in the chest that we recognize as anginal, he is subject to sudden unpredictable death unless the cause can be removed. Finding sclerosed or calcified coronary arteries on postmortem or fluoroscopic examination is an anatomic observation. Such a patient generally has had angina, but that is not necessarily true, just as the x-ray finding of calcification of the pericardium generally, but not always, signifies pericardial constriction. Whether there is actual constrictive pericarditis will be better told by discovering whether the venous pressure is elevated or the liver is engorged. In other words, one is a diagnosis of a functional and the other of an anatomical state.

PUZZLING ASPECTS OF ANGINA

Despite the ease with which the diagnosis of angina can be made, there remain many puzzling and in some ways conflicting aspects to the problem. The actual cause and site of the pain or distress is uncertain. Does it originate in the artery at the point of narrowing or spasm or is it due to distension of the vessel proximal to a point of spasm? Is it made in the muscle that is temporarily anoxic? It seems unsatisfactory to state, as is often done, that the pain is due to the lack of oxygen. The distress must be due to the presence of something, not to the absence of something. Is this lactic acid or some other metabolite? It seems that anoxemia has been used too readily as a cause of cardiac abnormalities. Patients may bleed to death, remain quite clear mentally until only minutes before the end and yet suffer no anginal symptoms. Under such circumstances there must be profound

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anoxemia of the myocardium without resulting heart pain.

Angina and Disbalance of Different Parts of the Heart: There are some features of angina that make one think that pain results if one local part of the heart is impaired or poorly irrigated while the rest of the heart is at least temporarily in better condition. If the entire heart were equally impaired or weakened, anginal distress might not result. May it not be true that the main part of the heart is contracting too well while a small portion is suffering? When the entire heart for one reason or another contracts feebly, the anginal state may disappear. We see a hyperactive contraction when we fluoroscope a thyrotoxic patient with angina. But when he is cured of the thyrotoxicosis and no longer has angina, the cardiac contractions are feeble. Patients at times lose their anginal pain as congestive failure develops or cardiac output decreases. Is the localized unhealthy part of the heart less labored in its activity and less painful as the remainder of the heart contracts less vigorously?

Some observations made by Sutton and Lueth[1] bear on this question. They applied a ligature around a coronary artery of the dog. Later in the unanesthetized state, traction of the ligature produced grimaces and other reactions that were transient and lasted while the traction was continued, which were regarded as comparable to anginal distress. The results were ascribed to coronary constriction and localized anoxemia of the heart. At a later date Katz and his co-workers[2] performed somewhat similar experiments in such a way that traction of the ligature did not produce any decrease in blood flow. He observed that the same grimaces resulted from this traction and concluded that the "discomforts or pain" in the dogs originated in the adventitia of the artery that was pinched and not from anoxemia.

Sudden ventricular fibrillation is generally thought to be associated with coronary artery disease and myocardial anoxemia. If the left coronary artery of a dog is ligated near its origin, ventricular fibrillation and death of the dog generally result in the great majority of instances. Some years ago Fauteux[3] found that if both coronary arteries were simultaneously ligated, ventricular fibrillation was not so likely to follow. The heart gradually failed and the animal died but was not so apt to develop this arrhythmia. There certainly was more anoxemia of the heart when both arteries were tied than when only one. Furthermore, he noted that if one coronary was ligated but the proximal portion allowed to bleed, ventricular fibrillation did not develop. He believed that localized tension of a coronary vessel was an important factor in the precipitation of ventricular fibrillation rather than ventricular anoxemia.

More recent work by Brofman, Leighninger, and Beck[4] emphasizes the importance of a disbalance of various parts of the heart in the production of pathologic behavior, and sudden ventricular fibrillation. The suggestions and intimations in these studies lend some support to the concept that an important factor in the production of some clinical features of coronary artery disease is the difference in the behavior of different parts of the heart.

Angina and Thyrotoxicosis: A frequent statement occurs in medical discussions that whatever decreases the demand on the heart improves angina. When a patient has angina and thyrotoxicosis, a cure of the hyperthyroidism lessens the angina often tremendously. The improvement is generally explained on the basis that the basal metabolism (oxygen consumption) is decreased, the work of the heart is lessened, and therefore the painful episodes disappear. This argument would only have merit if not only the work or demand on the heart were decreased but the oxygen or blood supply to the heart were not equally decreased. There is a lessened total cardiac output when the basal metabolism of such a patient falls from plus 45 per cent to plus 5 per cent and very likely a decrease in coronary flow as well. As far as demand and supply is concerned, the heart would be in better condition only if the decrease in demand were greater than the decrease in supply. Furthermore, the structural condition of the heart is essentially unchanged all day, and yet the attacks of angina in these cases come at rest without obvious cause: What occurs at that very moment to precipitate the attack of pain? It is difficult to comprehend this trigger mechanism in many instances of anginal pain at rest that occurs

in a great variety of cases. Is it due to the release of excessive adrenalin within the body at that moment?

Another puzzling observation in the behavior of anginal pain is the occasional abrupt response to antithyroid drugs when thyrotoxicosis is present. I have observed two instances where anginal spells that were recurring many times daily while the patients were in bed over long control periods, promptly vanished in several days on propyl thiouracil therapy. The dramatic improvement took place long before the basal metabolism had changed. The quick response resembled a neutralizing effect, as if the antithyroid drug acted on some toxic substance that was injurious to the heart. Although such experiences are unusual, they provoke speculation.

Angina and Body Position: The relation of posture of body to anginal pain is of some interest. We are all familiar with the explosive attacks of cardiac asthma or paroxysmal nocturnal dyspnea that characteristically occur in bed one or two o'clock in the morning. There is something about this mechanism that requires a few hours for its production. Apparently, there is a gradual shift of fluid from the extra- to the intravascular spaces with recumbency. The result is hemodilution, an increased blood volume, and other undesirable changes in the dynamics of the circulation. It takes some while for all this to become sufficiently embarrassing to produce distressing pulmonary congestion or edema in certain cardiacs. The patient quickly learns that relief may come more quickly if he sits or even stands. Patients who experience attacks of angina while recumbent likewise generally find that the pain will lessen or subside more quickly if they sit or even stand. Here the changes brought on by posture either in the production or the relief of pain occur abruptly, in seconds or minutes. A suggestion recently made by Vugrincic[5] may offer an explanation for this. The aorta with its arch and its descending portion may be likened to a cane. It would appear much easier (requiring less foot pounds of work) for the left ventricle to eject 60 cc of blood with each contraction when the patient is sitting or standing as it merely has to get the blood over the arch of the aorta and after that gravity helps to propel the stream to the trunk and lower limbs. When the patient is lying flat, although blood would reach the brain more readily, a much larger part of the left ventricular output is directed elsewhere and no aid from gravity is available for this purpose. Although there are other factors such as vasomotor tone that come into play in such problems, it seems quite likely that left ventricular work required to expel a given amount of blood is less in the upright than in the recumbent position. If this is true it would readily explain the rapid waning of anginal pain in some patients with the assumption of the upright position.

Angina and Carotid Sinus Stimulation: Another puzzling observation is the prompt relief of anginal pain that can often be obtained by carotid sinus stimulation.[6] Not long ago it was observed that anginal pain could be relieved occasionally by carotid sinus massage. I became interested in this phenomenon and found that it was a very satisfactory and distinctive test of anginal pain. After observation in hundreds of tests, it appeared that whenever stimulation of the carotid sinus was carried out while the patient had anginal pain and the heart slowed satisfactorily, the pain would stop or lessen instantly. I have had very frequent opportunity to observe anginal pain, as my presence or conversation with the patient often evokes a spell. When the pain would come, I would immediately stop everything else and ask the patient whether he was having his customary discomfort. I would apply the stethoscope to the precordium and ask the patient or an attendant nurse or physician to hold it in place. Then I would massage the right or the left carotid sinus for several seconds. Directly after this the patient would be asked whether the pain was *worse*. The purpose is to try to be misleading. In my experience, if good slowing takes place, the patient will almost always reply "The pain is gone." or "The pain is lessening." The amazing feature is that the effect on the discomfort takes place in seconds. Many patients have the same kind of reaction. When asked about the pain, they pause for a moment, seem to look into themselves, and then reply with surprise that the attack is over or waning. In some instances, as the heart rate increases again the pain returns and one can

repeat the procedure. In others the spell is over and does not return promptly. In one instance the pain actually vanished while the heart was not beating, a very long asystole having resulted from the carotid stimulation. It is of interest that when no slowing occurs the pain is rarely if ever affected. This peculiar phenomenon needs further study, but at the present moment it would appear that the test has diagnostic value. If carried out as above suggested and the patient has chest or arm discomfort which disappears or lessens in several seconds following ventricular slowing, it is almost certain that we are dealing with coronary artery pain. The test may be invalid during the severe pain of an acute coronary thrombosis though even here slight lessening of the pain may occur. A limited experience would indicate that other types of pain very rarely respond in a similar fashion.

When these observations were first made, in seeking for an explanation for such instant relief of anginal pain, the possibility of the release of spasm by a nervous reflex came to mind. Then when it was found that left arm pain quickly disappeared following right carotid sinus stimulation and that relief practically never was obtained if slowing did not result, some other explanation seemed more likely. It would appear that with the slowing of the heart the noxious catabolite (possibly lactic acid) or the "P" principle of Lewis[7] was washed out and less of it was formed by the fewer contractions. Inasmuch as most of the coronary perfusion takes place during diastole, with a slower heart rate, the irritating chemical could very well decrease in its concentration. This possible explanation is in accord with the clinical impression that anginal pain is quite rare with the slow ventricular rate of complete heart block even in the presence of considerable coronary sclerosis.

Angina and Physical Effort: Another puzzling feature of anginal pain is the frequent lack of relationship between the work performed and the development of pain. Although physical effort is by far the most common precipitating cause of anginal discomfort, it is amazing that so many patients can do very strenuous work all day long and yet not be able to walk one or two blocks in the street without having to stop for pain. The same thing is observed when patients tell us that they have to stop on the first hole of golf and then have no more trouble the rest of the game or have pain going to the train in the morning but have no more pain the rest of the day though they may walk greater distances. We know that the same effort is more difficult if undertaken directly after than before eating or in cold than in warm air. Another very important factor that may explain some of these apparent discrepancies is the speed of the activity. Does the golfer walk a little slower after having chest pain going to the first hole? Patients can walk a mile or more at a slow pace and yet have anginal pain on walking one hundred feet briskly. The weight of the clothes worn, whether the patient is carrying an additional package or is conversing while walking, whether the road is slightly upgrade,—all these are factors that may play a role. Even when all the known factors are considered, there remain in many instances striking discrepancies between the amount of effort and the production of pain. The actual foot pounds of work demanded of and performed by the heart does not appear to be the whole story.

Angina and Emotional Factors: It is well known that psychic and neurogenic influences play a role in the production of anginal pain. Attacks frequently are precipitated by emotional tension. Both pleasant and unpleasant thoughts and experiences may act as triggers in bringing on attacks. One may ask, in addition, whether spells may not occur as a result of a conditioned reflex. The frequent occurrence of attacks of angina under similar circumstances in the same individual, in which the physical or emotional factors do not appear to be sufficient, make one wonder whether something in the nature of a habit or conditioned reflex is involved. After a patient has developed attacks on walking to the garage in the morning on several occasions (though he may have no more spells the rest of the day) it is easier for the same thing to repeat itself and he may even develop a spell at the thought of going to the garage before he actually starts out. This concept needs much study for it may lead to an effective psychotherapeutic approach in some individual cases.

Puzzling Aspects of Coronary Sclerosis

There has been intense interest in a possible dietary factor as a cause of coronary artery disease. A good deal of evidence suggests that excessive ingestion of fats in certain parts of the world is responsible for the great prevalence of coronary disease in those areas. Another factor that is being suspected is the lack of physical exercise.

Diet and Exercise: However important these general influences may prove to be, it is still difficult to explain the peculiar localization of atherosclerotic changes to certain parts of the coronary arteries. There are many young males who die of coronary thrombosis who show a thrombosis in a particular part of the left descending coronary artery and yet have very little, if any, significant atherosclerosis in the remainder of the coronary tree or in fact elsewhere in the body. Why does the sclerotic process localize itself in the heart and moreover in one favorite part of a vessel? General causes like diet or exercise cannot account for this peculiar localization of the sclerosis. If a patient had jaundice in one finger, though there might be some disease in the biliary system or blood, one would look for some abnormality of the finger to account for the localization of the jaundice in that part of the body. Likewise, one ought to find some cause in the heart itself to explain the frequent limitation of advanced sclerosis to the vessels of this organ.

Hereditary Factors: Although there are many uncertainties about the nature of angina, we are sure there is a familial and hereditary factor. When we speak of a familial tendency to a certain disease, in final analysis there must be some peculiar structural or anatomic condition that is inherited. In many instances these structures have not been identified. These abnormalities may be differences in the number or nature of certain cells or granules within cells or other anatomic or chemical structures hitherto unknown. We do inherit specific physical attributes. May not the hereditary factor in early coronary disease be the inheritance of a peculiar architecture of the coronary vessels? A very slightly greater bend of the left descending coronary artery at a critical point might more readily become sclerotic from the repeated trauma of contraction and torsion that accompanies each systole. This sclerosis might not happen so readily if the individual inherited a different type of architecture of the blood vessels. Differences in the structure of coronary arteries in different people have already been described by Schlesinger.[8] Or the critical differences may be in the original thickness at birth of the endothelial lining of coronary arteries in the two sexes as described by Dock.[9] In a word, more minute and careful study of the normal coronary arteries and their variations is urgently needed. Very recently some work along this direction has been published and supports the concept that mechanical factors largely determine the localization of atherosclerosis in the heart (Texon).[10]

Bed Rest in Coronary Thrombosis: Another peculiarity concerning coronary disease that bears some comment is the attitude of the physician towards the treatment of acute coronary thrombosis. Some 40 years ago it became the custom to treat this acute condition by keeping the patient in bed for six weeks. The period was later often shortened by a week or two, but strict bed rest was still rigidly enforced. I confess that ever since the first case I recognized antemortem in 1916 I was partly responsible for establishing this method of treatment. However, during the last 20 years there has appeared enough clinical and laboratory and physiologic evidence to invalidate this view. We know now that the heart works a good deal more with the patient recumbent in bed than when sitting in a chair. Patients with left ventricular failure and especially those with paroxysmal nocturnal dyspnea have known for centuries that they are better off in a chair than in bed. I will not go into all the recently accumulated evidence to support this concept. However, there is no doubt that if we want to rest the heart this will be best accomplished if the patient sits in a suitable chair with the feet down rather than lying in bed. The difficulty is that the public has become so terrified by the sudden death that may occur with heart disease and has been so impressed by the greater risk if the patient is not in bed that the physician has not the courage to mend his ways. All is forgiven if the patient dies in bed, cardiacs are supposed to die in bed. However, if the victim succumbs out of bed the

physician is blamed. We are not blamed for all those who have been lost by keeping them in bed. I feel quite certain there will be a lesser total mortality in acute coronary thrombosis if patients are routinely kept out of bed most of the day (unless shock is present) than if kept in bed.[11] This does not mean earlier ambulation or allowing such patients to do more in a chair than you would have them do in bed. Nor do I mean that they need to be lifted back and forth from bed. They are merely guided by one or two attendants just as one would do to have them get onto a commode—a practice that most physicians now permit instead of the use of the annoying bedpan.

Prognosis in Coronary Disease: A final puzzling point is the differences in statistics that appear in medical publications concerning prognosis in coronary disease. Insufficient attention is paid to differences in sampling of the material. In estimating the mortality of acute attacks of myocardial infarction, one should consider whether the cases are consecutive cases seen in a large general hospital or seen in homes. Hospital practice is weighted with the more severely ill. Are the cases those seen by a consultant? The more critically ill the patient, the more likely it is that the consultant will be called. Does the consultant answer calls promptly? If, for one reason or another, he has to delay seeing patients for several days frequently he will obviously fail to see those who die the first few days after the onset of an acute coronary thrombosis. If the one reporting the study includes ambulatory cases first seen in the consultant's office years after the original attack of myocardial infarction, such cases should not be included in estimating the average or expected life expectancy after first attacks. The reason for this is that these ambulatory cases have already lived a certain interval of time (months or years) before coming to the consultant and could not have been included in a study of consecutive cases if they had died shortly after recovery from the attack. They do not belong in a study of consecutive cases recovering from their first acute attack. This kind of study could only be carried out by a general practitioner who sees all cases from the very onset until the very end.

Also the question of accuracy and criteria of diagnosis comes up. If patients with myocardial infarction who had had no major clinical episodes that are recognized (even correctly) by an expert in electrocardiography are included, a different group of patients is being studied than if the customary clinical features of an acute coronary thrombosis are necessary criteria. Furthermore, the general age of the population from which the experience is gathered is of prime importance. The average age at death from coronary thrombosis in the United States Army during the Second World War may well have been 28 years. This may also be the age at death from measles merely because the overall age of the population studied was young.

The care with which the medical history is taken is of utmost importance and has an effect on the estimation of length of life with angina pectoris. One physician obtains a history that since a certain date (January 1940) a particular patient has had definite anginal pain. He outlines a course of treatment, follows the patient for years, and finally finds that he lived seven and one-half years from the onset of symptoms and died July 1947. As it happened, another physician also saw the same patient during his lifetime and because of more direct and intensive questioning learned that mild but definite anginal symptoms really began January 1937. The second physician after obtaining the same history as the first may have put a question like this: "When did you ever have any discomforts, even mild ones, like these before?" The patient may have paused and replied, "Now I recall that three years before I had these funny feelings in my chest and left arm in cold weather but I paid little attention to them." This difference in history taking makes a difference of three years. One physician did not treat the patient any better than the other even if his figures indicate that the patient lived three years longer. One can readily see the great difficulties in interpreting some of the statistical studies of coronary disease.

Conclusion

The above illustrates some of the puzzling aspects of the problem of angina pectoris and coronary sclerosis. There are many others. It is obvious that much is unknown concerning

this subject though it has been studied for many generations. It will require additional effort and possibly new investigative approaches. More difficult problems have been solved. We therefore can look hopefully to the future.

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"Mild" Myocardial Infarction

Clinical Features and New Method of Management*

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FOR MANY years it has been the almost universally accepted practice to prescribe several weeks of rest in all cases of acute myocardial infarction regardless of the severity of the attack. The carefully done autopsy study of the histologic healing rate of acute myocardial infarction by Mallory, White, and Salcedo-Salgar[1] gave support to this empirical practice. However, cases studied in the necropsy table do not take into consideration "mild" cases that survived. Estimates of the duration of necessary treatment based on autopsy material are not necessarily applicable to "mild" cases. It seems logical to postulate that "mild" cases need less treatment than more severe cases. Standard textbooks of medicine and cardiology recommended from four weeks to two months of rest.[2–5] Harrison[4] and Friedberg[5] have suggested that such prolonged rest may not be necessary in all instances and advise that the treatment be individualized according to the severity of the attack. This principle seems reasonable and is followed in nearly every clinical condition except acute myocardial infarction.

We have recently described a series of cases[6] in which the electrocardiographic evidence of infarction was found only in leads taken from the upper sternal and parasternal regions. Conventional leads in these cases usually showed changes suggesting myocardial ischemia only. In this series of high anterior infarctions there were no deaths. A review of the clinicopathologic findings in the large number of autopsied cases of myocardial infarction described by others disclosed that a small proportion of these hearts contained scars of healed high anterior infarcts. However, all of these cases had died from subsequent, larger infarcts located in more caudal portions of the myocardium. It is clear that high anterior infarctions are relatively small, do not give rise to a severe clinical course and by themselves are rarely fatal.

Furthermore, some years ago we showed that simple, purely subendocardial infarcts may not reveal themselves in the clinical electrocardiogram.[7] Nevertheless, it is now possible to diagnose even small lesions of this type. The clinical course in such cases is uniformly benign.

The present communication will attempt to show that it is possible to individualize treatment in acute myocardial infarction. It is clear that modern diagnostic methods provide a means of detecting many "mild" cases which were previously overlooked or mistaken for coronary insufficiency. Furthermore, it will be seen that certain criteria can now be established which permit instances of "mild" myocardial infarction to be differentiated from more "severe" cases. Such "mild" cases may then be successfully managed with much less immobilization of the patient and much less economic and psychologic disturbance than has been previously thought possible. In this communication the term "rest" is meant to include both bed-rest and arm-chair treatment.[8]

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The relative merits of the two methods of management is not under consideration here.

For some time it has been our practice to classify patients with acute myocardial infarction into "mild," "moderate," and "severe" categories. The clinical data required for the classification is obtained during the first two weeks of illness. Classification is not attempted until this period has elapsed. Such a classification presents certain difficulties, particularly in differentiating between "moderate" and "severe" cases. It appears considerably less difficult to detect cases of the "mild" type with a high degree of accuracy. It is with this group that this study is particularly concerned.

Since the clinical severity of cases of myocardial infarction depends largely on the size of the infarct, it is obvious that no sharp line of distinction can be drawn between "mild" and "moderate" cases on the one hand and between "moderate" and "severe" cases on the other. Infarcts can be of any size, causing necrosis of masses of muscle varying in weight from a fraction of a gram to 200 g or more. Thus, some cases will be difficult or impossible to classify into one distinct category. Yet it is surprising how easily recognizable are most of the typical "mild" cases, using the criteria which follow.*

Criteria for Classification of Cases of Myocardial Infarction

(A) *The "Mild" Case:* The typical patient with a "mild" myocardial infarction is young or middle-aged. He is usually vigorous, active, and apparently in excellent health. He has never had a previous myocardial infarct or any other clinically evident heart disease. There has been no hypertension, diabetes, or other significant chronic illness.

The pain associated with the infarction is of a relatively short duration. It usually responds readily to medication and does not recur. Shock is not present either at the onset or later.

Temperature elevation following the attack is absent or minimal and of short duration. Leukocytosis is mild and the erythrocyte sedimentation rate only slightly increased. Serum transaminase levels are only moderately elevated. The heart does not become enlarged, gallop rhythm does not occur, and signs of congestive failure do not appear at any time during the course of the illness. Significant arrhythmias are not observed.

Within a day or two after the onset the patient looks and feels well. Unless he has been seriously frightened by the attack, he is usually eager to get up and return to work.

It should be obvious that the clinical appearance of the patient and his sense of well being are the most important factors to be considered among the criteria for classification. However, it must be emphasized that all the criteria described above must be fulfilled in order to justify classification of any case as "mild." The importance of fulfillment of all these criteria becomes clearer when it is realized that a small myocardial infarct can result in a very severe or fatal clinical course if it occurs, for example, in an old or debilitated individual, or in a patient who has already had one or more previous infarctions. A close analogy can be drawn between such a clinical picture and that which results from a small patch of pneumonitis. In a young, otherwise healthy patient, such a lesion may result in a very mild illness, during which the patient may not even go to bed. In an older debilitated individual, however, the same lesion may kill the patient. Therefore, the entire clinical picture must be taken into consideration in deciding upon the proper classification of cases of myocardial infarction. Expressed in another way, it may be said that we try to classify the case, not the infarct.

(*B*) *Severe Case:* In contrast, patients who have severe or repeated bouts of pain, marked drops in blood pressure, marked leukocytosis, high elevations of the erythrocyte sedimentation rate and of serum transaminase levels, high and prolonged temperatures, congestive failure and arrhythmias requiring treatment are classified as "severe" cases. Patients with diabetes or hypertension are usually found in this group.

* It is probable that many cases of "mild" myocardial infarction have been diagnosed "coronary insufficiency." While we have no doubt that the syndrome of coronary insufficiency is not uncommon, we believe that this term should be applied only to cases in which there has been a clear precipitating factor such as shock, hemorrhage, arrhythmia, etc., which are attended by hypotension and reduction in coronary flow below the metabolic requirements of the heart.

(*C*) *Moderate Case:* Cases intermediate in severity between the latter two groups are classified as "moderate." Such a classification is by necessity quite arbitrary. Many cases which fulfill some of the criteria for a "moderate" classification will have some of the conditions necessitating a "severe" classification. Such borderline cases are difficult if not impossible to classify. For example, we have seen instances in which the symptoms fulfilled all the criteria of a "mild" attack except that the erythrocyte sedimentation rate was markedly elevated or the leukocytosis was in excess of that allowed by our criteria for the "mild" category. Indeed, 7.5 per cent of our cases were found difficult to classify. Most of these fall in a group intermediate between "moderate" and "severe." The mild cases are more readily detected; it is the identification of this latter group which is the primary purpose of this classification. It would appear that the degree of elevation of serum transaminase is the best laboratory index of severity of myocardial infarction.

The electrocardiogram is of course a most useful diagnostic method in the great majority of cases of myocardial infarction. It is, however, subject to limitations. If the tracing is normal, myocardial infarction is not excluded. Whether the tracing is normal or abnormal, it rarely provides evidence concerning the severity of an infarction.

Classification of 200 Consecutive Admissions to the Hospital for Myocardial Infarction

In order to test the workability of the classification, the charts of 200 consecutive patients admitted to Cedars of Lebanon Hospital for myocardial infarction were reviewed and classified. Patients who died were omitted from this group since the fatal cases were studied separately and will be discussed later in the paper.

Using the clinical data recorded during the first two weeks following admission to the hospital and the criteria described above, 15.0 per cent of the cases were classified as "mild." 18.5 per cent were "moderate" cases, 59 per cent were "severe" cases. Seven and one-half per cent of the cases could not be classified.

These figures will no doubt vary in different clinics and hospitals. It is probable that the percentage of "mild" cases is a falsely low figure, since many small infarctions yield such relatively minor symptomatology that the patient does not seek medical attention or, in some cases with atypical symptoms, the infarction may remain undiagnosed. In some situations when the patient is seen at home and the infarction appears to be mild, the patient refuses hospitalization. Hence, it is believed that the incidence of "mild" cases is actually much higher than that found in this series of hospitalized cases.

Incidence of "Mild" Cases in a Series of Fatal Myocardial Infarctions

The clinical charts of 400 patients who died of acute myocardial infarction at the Cedars of Lebanon Hospital during a period of six and one-half years were reviewed. Of these, 200 were autopsied and 200 were not. Using only the clinical data observed during the first two weeks in the hospital, these 400 cases were classified according to the outlined criteria. The study was limited to patients whose primary diagnosis was myocardial infarction, and who died of this condition or its complications. Patients in whom myocardial infarction developed as a complication of other conditions such as surgical shock, malignancy, etc., were excluded, as were patients who died within 36 hours following admission to the hospital because the period of observation was too short for classification by our criteria.

In this series of 400 fatal cases we were unable to find a single instance which fulfilled the criteria described for "mild" cases. In such a series it was anticipated that the great majority of cases would manifest "severe" symptomatology but it was surprising that not even one patient presenting a "mild" clinical picture died from myocardial infarction. *Thus the immediate mortality rate in cases classified as "mild" myocardial infarction seems nearly nil.*

It is likely that an occasional patient in this category will die within two weeks after the onset as a result of an extension of the originally small infarct, or develop a new infarct soon after the first. Death may also occasionally

result from an otherwise "mild" infarction which involves the A-V node causing Stokes-Adams attacks, or from a small lesion which acts as an irritable focus resulting in a serious arrhythmia such as ventricular tachycardia or fibrillation. Although such cases were carefully looked for, we found none in the series studied. It seems safe, therefore, to conclude that these "mild" cases have an extremely low immediate mortality, certainly less than one per cent.

Treatment of "Mild" Cases

The ultimate purpose of attempting to identify "mild" cases is to try to improve upon the usual methods of management of these patients. In view of their excellent prognosis, it seems neither necessary nor desirable to restrict the activities of these patients to the extent warranted in more serious cases. For the first two weeks after the onset, the patient is treated in the usual manner, either in bed or in a chair. At the end of this period, if the case is believed to fall into the group of "mild" infarctions, a gradual resumption of normal activities is begun. Every attempt is made to avoid stressful situations, emotional as well as physical. If no untoward incidents occur, the patient is allowed to return to work under the close supervision of the attending physician. In general, the first day the patient is allowed to work for one hour. The second day he is allowed two hours, and the third day three hours. No further increase in working time is permitted until the end of the first week when a complete re-evaluation is made by the physician. If the situation is progressing satisfactorily, the patient is allowed to increase his work by one hour per day during the second week. He is then re-examined at weekly intervals for the next month. If at any time there appear unfavorable signs of symptoms, the patient is returned to bed and the entire situation re-evaluated.

It should be emphasized that such short term therapy is considered only in patients with "mild" myocardial infarctions. If the classification is questionable in any given case, the patient is treated in the conventional manner. It is also inadvisable to depart from the usual method of treatment if the patient or his family is apprehensive about early resumption of activity.

Observations

The authors have had the opportunity to observe or treat 22 patients with "mild" myocardial infarctions whose duration of treatment was less than the number of weeks conventionally prescribed. Seven of these patients have been followed more than one year. While final conclusions cannot be drawn on the basis of this small number of cases the obvious psychologic, economic, and physical benefits observed in these patients as the result of a shortened period of therapy and the total absence of any harmful effects suggest that the subject is worthy of further consideration and investigation.

Case Histories

Case 1. A.B. This 74-year-old retired dentist was first seen by one of the authors in 1952 for treatment of congestive heart failure. He stated that 25 years previous, in 1927, he had been awakened early in the morning with severe precordial pain radiating to both arms, accompanied by a feeling of suffocation. The pain lasted for several hours, but he thought it was acute indigestion and did not consult a physician. The following day he went to work. Two years later he suffered a similar attack of pain. Following the second episode of pain, he developed classic angina pectoris. Over the next few years he saw several well-known cardiologists who agreed that the patient had arteriosclerotic heart disease and had incurred one and probably two myocardial infarctions in the past. Electrocardiograms showed combined posterior and antero-septal infarctions; there were QS waves in standard leads 2 and 3 and in precordial leads V_2, V_3, and V_4. In 1952, the patient was treated without improvement by administration of Iodine-131. He continued to have angina pectoris and chronic congestive heart failure and died in 1956.

This patient suffered several separate myocardial infarctions. Because of his failure to consult a physician at the time of his first attack in 1927, he was not treated with bed rest. Yet, he survived for 29 years following his first attack and died at the age of 74 of congestive heart failure. A survival of 29 years after the initial infarction would seem to negate the possibility that the lack of bed rest shortened this patient's life expectancy.

Case 2. C.D. This 59-year-old white female was first seen in 1949 at the age of 52 years complaining of nervousness, palpitation and vague aching in the chest. In the preceding several years she had consulted numerous physicians who made no diagnosis other than anxiety reaction. Her complaints were centered about chest

pain, palpitation, and occasional episodes of tachycardia which were usually related to emotional upheavals. Physical examination revealed a 52-year-old white female who appeared tense and high strung. The blood pressure was 118/78; the pulse was 110. The remainder of the physical examination was essentially negative. Electrocardiograms were considered to be abnormal but not diagnostic. A serum protein-bound iodine was 8.3 μg per 100 cc and the patient was considered to have mild hyperthyroidism. She was treated with Iodine-131 and her complaints of palpitation and tachycardia subsided.

During the last eight years she has continued to complain of nervousness and occasionally poorly located aching in her chest unrelated to exercise. As part of a general check-up, a standard 12-lead electrocardiogram with an additional multiple-lead exploration of the chest was undertaken. Much to everyone's surprise, it was evident that this patient had an old high anterior myocardial infarction. It was impossible to tell when the infarction occurred as the patient has had multiple complaints not typical of any specific disease for many years. Her standard 12-lead electrocardiogram has remained unchanged; QS waves indicative of myocardial infarction are seen only in the first three intercostal spaces overlying precordial positions V_1 through V_4.

This patient with atypical complaints had incurred a myocardial infarction sometime in the past which went unrecognized until exploring leads were taken in high intercostal spaces. Since here myocardial infarction was undiagnosed, she did not receive any therapy at the time of her infarction. To date, there is no evidence that she has suffered any ill effects from her lack of treatment at the time of the acute infarction.

Case 3. E.F. This 55-year-old physician had no cardiac symptoms until the age of 47 when he suffered an attack of severe oppressive substernal pain which radiated down his left arm. The pain was quite intense and he went to bed after taking morphine sulfate grains 1/4. Electrocardiograms taken during routine annual physical examinations had always been completely normal. An electrocardiogram taken following the substernal pain revealed a left bundle branch block. The left bundle branch block has persisted to date.

The patient remained in bed at home for a period of ten days and then because of heavy financial pressure, he returned to full time private practice of medicine. For a period of one year following the acute attack, he noted occasional episodes of angina pectoris but he has had no angina during the last eight years. Presently, he is engaged in a busy private practice and has no limitation of physical activity.

This patient is an example of how financial necessity can force a patient to return to full-time work shortly after an acute myocardial infarction. Since this patient has no limitation of physical activity, as demonstrated by his ability to carry on a busy private practice for the past nine years, there is no reason to suppose that the brevity of the period of rest at the time of the acute infarction was in any way harmful.

Case 4. G.H. This 42-year-old physician was playing tennis in 1952 when he was suddenly seized with "constricting precordial distress." The pain did not radiate but persisted for about two hours and then gradually subsided although the patient was aware of some "sensation" over the precordium for the next seven days. An electrocardiogram taken a few hours after the acute attack showed inverted T waves in V_5 and V_6 but was otherwise noninformative. His erythrocyte sedimentation rate rose to a high of 25 mm/hr (Wintrobe method) and then gradually returned to normal over the next three weeks. There was no ST elevation in any of the tracings indicative of acute nonspecific pericarditis which in many instances is confused with acute myocardial infarction.

The patient was seen in consultation on the day following the onset of pain. He was comfortable but markedly apprehensive. This was certainly understandable in view of the fact that he was a young physician who had recently entered private practice, was deeply in debt, and sorely troubled about the financial aspects of a prolonged illness and convalescence.

Since he had suffered a very "mild" infarction and the emotional trauma of convalescence was so marked, it was felt that this patient would be harmed more by the conventional prolonged regimen than by earlier gradual resumption of his usual activities. Hence, he was reassured and instructed to get out of bed and move about his house as much as he wished. By the end of the week, he was completely asymptomatic and gradually returned to his practice.

Since the acute episode five years previous, this patient has had no recurrences of pain and has carried on a very busy private practice without any limitation of his physical activities. He is free of cardiac symptoms and there is no reason to suspect that the shortened period of therapy was in any way harmful.

Case 5. I.J. This 48-year-old man presented himself in 1952 complaining of the recent onset of angina pectoris two weeks previously. An electrocardiogram taken one week previously was reported as negative. An electrocardiogram taken on the day the patient was first seen by one of the authors showed inverted T waves in lead I, aVR and V_1 to V_4.

The patient was hospitalized with a diagnosis of acute myocardial infarction. Physical examination on admission revealed a blood pressure of 180/110 but was other-

wise negative. On the next day the blood pressure became normal and remained so thereafter. The erythrocyte sedimentation rate was 15 mm/hr (Wintrobe method) and then rose to 32 mm/hr. The temperature rose to a maximum height of 100° F on the second hospital day and then over the next two days gradually returned to normal. After the first hospital day, the patient became completely asymptomatic and was discharged after ten days of hospitalization.

Following his 10-day hospitalization this patient was allowed increasing activity under close supervision. Two weeks after his discharge from the hospital, he was allowed to return to work. He has been seen at regular intervals since that time and has been asymptomatic since the original attack in 1952.

This patient is another example of a benign course following a short-term treatment of an acute "mild" myocardial infarction. It is now five years since his initial attack and he is leading a full, active, asymptomatic life.

CASE 6. K.L. This 45-year-old white male was admitted to Cedars of Lebanon Hospital about 1 a.m. on March 6, 1956; earlier in the night he was awakened from a sound sleep by severe left parasternal pain without radiation. The pain was relieved by Demerol® and did not recur thereafter. The blood pressure on admission was 110/70 mm Hg and the remainder of the physical examination was essentially negative. The serum transaminase rose to a high point of 72 units on the second hospital day. The white blood count was 13,110 on the day of admission and then gradually returned to normal levels. The electrocardiogram shortly after admission showed progressive decrease in the height of R waves from V_1 to V_4 in the first two intercostal spaces.

The patient had no further pain after the original attack and convalesced uneventfully. He was discharged on the seventh hospital day and instructed to rest at home for an additional week. He was then allowed to return to work on a part time basis under close supervision. He has been seen at frequent intervals and has been completely asymptomatic since. He is now working full time as a salesman with no limitation of physical activity.

CASE 7. M.N. This 42-year-old physician was sitting quietly at a conference when he was seized by severe substernal pain which radiated to his jaw, both ears, and the right scapula. This was accompanied by profuse sweating. There was no nausea or vomiting. After 30 minutes, he was given demerol intramuscularly, and the pain gradually subsided and did not return. An electrocardiogram was taken at that time and was reported normal except for a low T wave in lead aVF. Over the next several days, the T wave in aVF increased in amplitude. Otherwise, there was no change in the electrocardiogram and it was considered to be within normal limits.

The patient was seen in consultation by several cardiologists who agreed that the patient suffered a "mild" subendocardial infarction. His white blood count rose to 15,000 and then fell to 7,000 within seven days of the pain. No ST elevation indicative of pericarditis was seen in this patient. Since the infarct was small and the patient was a tense, dynamic individual, it was felt that he should be allowed early activity. He was allowed out of bed on the third hospital day and sent home on the thirteenth hospital day. He had an uncomplicated and uneventful convalescence and is now back in full time private practice.

It is noteworthy that none of the above seven cases showed untoward effects as a result of the shortened period of treatment. On the other hand, all of them derived the benefit of early return to their usual activities. Case 1 had survived for 29 years following his initial myocardial infarction, and the remaining six patients are alive and well at this time. None shows any evidence of cardiomegaly, ventricular aneurysm, or congestive heart failure.

CARDIAC RUPTURE

The danger of rupture of the myocardium following a recent infarction is often cited as the main reason for insisting routinely on prolonged rest in order to provide enough time for the development of a firm scar.[1,9] The studies of Friedman and White[10] and Jetter and White[11] seem to substantiate the belief that early resumption of activity increases the incidence of cardiac rupture or of aneurysm formation. It is well known, however, that the great majority of cases developing these complications also have hypertension. This, ipso-facto, excludes them from the group of "mild" infarctions. Furthermore, clinical evidence indicates that even in severe cases cardiac rupture rarely occurs later than two weeks after infarction. In "mild" cases, the risk of rupture after two weeks of rest is nil. Since our plan of management during the first two weeks does not differ from the conventional, the danger of cardiac rupture has passed by the time increased activity is permitted.

The rarity of cardiac rupture later than two weeks after infarction suggests that this period

of time is sufficient for the development of a strong scar. In view of the importance of this subject, it is strange that heretofore no attempts have been made to measure experimentally at various stages the relative strength of such scars under conditions simulating human hemodynamics. It is obvious that histologic studies alone are inadequate for this purpose.

Experimental Studies: In an effort to secure this information and thus to estimate the relative danger of rupture of a "mild" infarction, the following experiment was undertaken in 29 mongrel dogs.

A small left ventricular branch of the anterior descending coronary artery was ligated with silk sutures through a sterile left thoracotomy incision in 20 dogs. In the remaining nine, the anterior descending artery was ligated at the junction of the proximal and middle one-third. Three dogs died postoperatively. Two weeks after the application of the ligature the 26 surviving animals were sacrificed and the hearts were extirpated.

The left ventricle was cannulated by retrograde insertion through the aorta. The cannula was connected to the water-bottle pressure system to facilitate the introduction of fluid under pressure. All vessels entering or leaving the heart, other than the aorta, were clamped off. Pressure was readily directly from a U-shaped glass mercury manometer. Fluid was then pumped into the left ventricle to determine at what pressure the infarcted site would rupture.

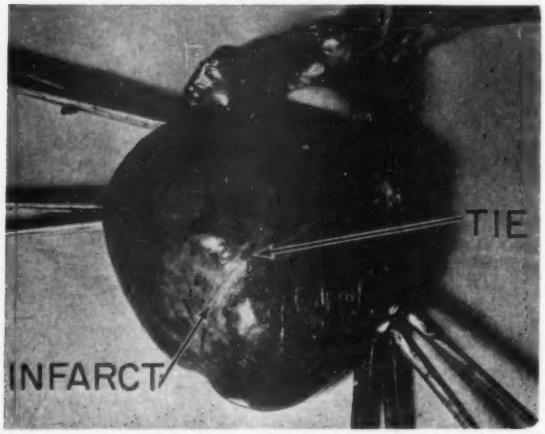

Fig. 1. An epicardial surface view of a transmural myocardial infarction. A ligature is seen around the anterior descending branch of the left coronary artery and the borders of the infarction as seen on the epicardial surface are outlined by a broken line. Although the intraventricular pressure was 500 mm Hg at the time this picture was taken, the area of infarction is clearly intact and there is no ballooning of the infarcted site suggesting the presence of a ventricular aneurysm.

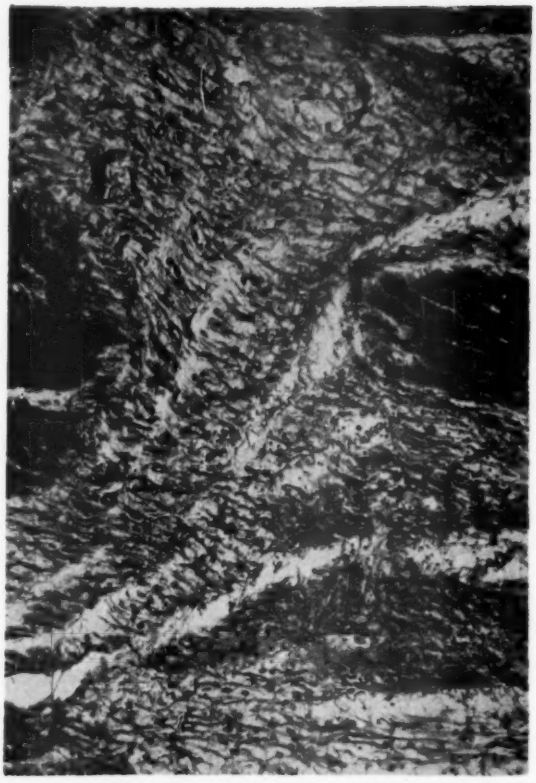

Fig. 2. A photomicrograph of a patchy myocardial infarction stained with hematoxylin and eosin. Note the large amount of dense fibrous connective tissue surrounded by viable myocardium. This infarct withstood an intraventricular pressure of 650 mm Hg. At that pressure, the left auricle ruptured and the infarct remained intact.

Results: In all dogs, except one, including those with moderately large areas of infarction, the infarcts remain intact even under extreme pressures. It was found that at high pressures either the right or left auricle would rupture while the infarcted ventricle remained intact. In one dog, the experiment was discontinued at 1,200 mm Hg with the infarct still unpunctured. It was interesting to note that in no instance did the infarcted sites show any sign of ballooning. This would indicate that under the conditions of this experiment none of these areas were potential aneurysms. Figure 1 shows an infarct under a pressure of 500 mm Hg. Although pressures up to 1,200 mm Hg were employed, there was only one instance in which the infarcted site leaked fluid (Table I). This isolated case was a large transmural infarction which leaked a very small stream of

TABLE I

Effect of Increased Intraventricular Pressure on Experimental Myocardial Infarction

Group I (Ligature of small left ventricular branch of anterior descending artery)	Type of infarction	Maximum pressure attained (mm Hg)	Site of rupture
Dogs			
1	No infarction	600	Right auricle
2	Small subendocardial	720	Right auricle
3	Patchy	800	Left auricle
4	Small subendocardial	700	Left auricle
5	No infarct	400	Left auricle
6	Small subendocardial	1200	No rupture
7	Died postoperatively		
8	Small subendocardial	580	Left auricle
9	Died postoperatively		
10	Small subendocardial	700	Left auricle
11	Large patchy	700	Infarct leaked small stream at 500 mm Hg. Right auricle ruptured at 700 mm Hg
12	No infarct	500	Left auricle
13	Subendocardial	520	Right auricle
14	No infarct	400	Right auricle
15	Patchy	600	Left auricle
16	Patchy	900	Left auricle
17	Patchy	440	Right auricle
18	Patchy	700	Left auricle
19	Subendocardial	680	Right auricle
20	Died postoperatively		
Group II (Ligature of anterior descending branch of left coronary artery in middle one-third)			
Dogs			
21	Large transmural	550	Right auricle
22	Large anteroseptal transmural	580	Left auricle
23	No infarct	680	Left auricle
24	Large patchy	680	Right auricle
25	Transmural	550	Right auricle
26	Patchy	600	Right auricle
27	Large transmural	700	Left auricle
28	Patchy	720	Right auricle
29	Large patchy	580	Right auricle

fluid at 550 mm Hg; at 700 mm Hg the infarcted site remained intact but the right auricle ruptured. *At pressures comparable to intraventricular pressures encountered in humans, no leakage of fluid occurred in any of the hearts.*

The infarcted areas were then sectioned and studied microscopically (Fig. 2 shows a typical area of infarction). Firm fibrous connective tissue is seen surrounded by viable myocardium.

On the basis of these experiments, it is clear that small areas of uncomplicated myocardial infarction appear to undergo complete healing and form surprisingly strong scars within two weeks after the vascular occlusion. Admittedly,

experimental infarcts in normal dog hearts cannot directly be compared with spontaneous myocardial infarctions in diseased human hearts. However, the remarkable strength of the infarcts demonstrated in the dogs strongly suggests that two weeks following a "mild" infarction the patient is left with a myocardial wall much stronger than previously estimated. These experiments thus confirm clinical experience and indicate that after a lapse of two weeks cardiac rupture or aneurysmal dilatation is very unlikely to occur in cases of "mild" infarction.

Discussion

The management of patients with acute myocardial infarction has for many years been standardized and inflexible. In patients with essential hypertension the treatment varies, depending on the severity of the situation. Certainly no one treats the milder forms of hypertension in the same manner as the malignant. But in spite of the established practice in most diseases of adapting the therapy to the individual case, the inclusion of many weeks of rest in the treatment of acute myocardial infarction regardless of severity has become so firmly established that most physicians do not even consider alternate methods of treatment.

The term "mild" as used in reference to an acute myocardial infarction was first employed by Herrick[12] in 1912. In referring to the symptomatology resulting when a small "twig" of a coronary vessel has become occluded, he drew an analogy to the "small" stroke resulting from occlusion of a small cerebral vessel.[13] The analogy is indeed apt. Occlusion of a small coronary vessel most often results in few clinical symptoms unless a strategic structure such as the A-V node is affected, just as a small cerebral vascular occlusion fails to yield dramatic clinical signs unless a cardial center such as Broca's speech area is involved.

All other things being equal, it would appear that the severity of the clinical picture in acute myocardial infarction is dependent largely upon the amount of tissue necrosis. If a very few grams or less of myocardium become necrotic following thrombosis of a small coronary twig in a young, otherwise healthy individual, the clinical manifestations are apt to be very mild or may be overlooked completely; the mortality is usually less than 1 per cent. On the other hand, if most or all of the left ventricle, involving perhaps 200 g of myocardium, becomes infarcted after closure of a large coronary artery, the mortality will be virtually 100 per cent. It should be remembered, however, that an originally "mild" case may become "severe" as a result of extension of the infarct or the occurrence of a new infarction.

We have separated acute myocardial infarction into three categories of severity, namely, "mild," "moderate," and "severe." It must be emphasized that such a classification in no way implies that even a very small acute myocardial infarction is not of great importance. Justification for such a classification is based upon the premise that while all infarctions are of prime significance, they do not all require a standard, uniform, inflexible therapeutic regimen. Classification of a given case outlined in this paper is based on clinical data collected during the two weeks immediately following the myocardial infarction. Classification is not attempted at the time of admission to the hospital. The criteria used for classification are arbitrary and other clinicians may wish to establish their own.

A review of the charts of 200 surviving patients who had been admitted to the hospital with a diagnosis of acute myocardial infarction, revealed that by the end of the first two weeks following the infarction, 15 per cent of the cases could be classified as mild. It seems obvious that this percentage is falsely low. Many patients with mild infarction with few and unimportant symptoms fail to seek medical attention. In some cases with atypical symptoms, the infarction may remain undiagnosed.

A review of 400 clinical charts of patients who died of myocardial infarction showed that prior to the time of death none of these cases could have been classified as "mild." It is astonishing to note that no cases classified as "mild" died during hospitalization.

Since the immediate mortality rate in acute "mild" infarction is so low, the question may

be raised as to the necessity or advisability of keeping these patients on prolonged rest as is done in the treatment of moderate and severe cases.

The reasons commonly given for prolonged rest are the dangers of cardiac rupture, ventricular aneurysm and the length of time required for healing of infarcts as demonstrated by White and his associates.[1] As to the latter, histologic studies of recent infarcts are available only in severe cases. Cases which qualify as mild within our classification do not come to autopsy.

Of the 200 autopsied cases studied, the large majority fell into the "severe" category clinically and the remainder were of the "moderate" group. The "mild" infarctions were conspicuous by their absence. Hence, histologic healing rates as estimated from autopsied materials do not appear to be directly applicable to patients with "mild" myocardial infarctions who seldom have a fatal course.

The danger of cardiac rupture in "mild" cases appears to be practically nil. As shown in a comprehensive review by Oblath and his group[14] postinfarction rupture occurred most frequently in hypertensive patients. Generally, the necrotic zones were of the large transmural type. Cases with such massive through-and-through infarctions, often with hypertension, would be excluded from the "mild" category. Our deliberate attempts experimentally to rupture infarcted areas two weeks after coronary artery ligature indicate that in the dog, by the end of 14 days, the infarcted area is healed and remarkably strong (Fig. 1). This finding is in keeping with the clinical observation that postinfarction rupture is very rare after the first two weeks, especially after "mild" infarction.

The occurrence of ventricular aneurysms following myocardial infarction is most commonly observed in patients with hypertension and in those with large through-and-through infarcts. None of our patients developed an aneurysm, and no ballooning of infarcted areas was seen in our experimental animals even at pressures far above any levels clinically possible. It is realized that the experimental evidence derived from animal experiments can do no more than support clinical experience. Carefully controlled clinical observations should be given more weight. In this regard, experimental and clinical evidence is in complete agreement.

A number of other questions may legitimately be raised concerning the advisability of early activation of patients with "mild" infarction. For example, will a patient treated for less than the usual period be more likely to develop an extension of his infarct, or to develop a new one soon after the first? Brummer *et al.*[15] believe that early activation of most patients with acute myocardial infarction, including severe cases, is not attended by increased immediate risk. Irvin and Burgess[16] feel that two weeks of bed rest is adequate for most patients with acute myocardial infarction. Thus far there is no conclusive evidence for or against these possibilities. No extension or immediate new infarction occurred in the cases observed by us, but experience is still too limited to provide a definite answer to this question.

The same situation exists with regard to the development of arrhythmias. Whether arrhythmias will be most common in patients treated with shorter periods of bed rest cannot be definitely predicted. No arrhythmias were observed in our "mild" cases; however, here again experience is limited. Other complications of myocardial infarction such as congestive heart failure and cardiac shock do not occur in cases properly classified as "mild" infarction.

Thus it would seem that early activation of "mild" cases of myocardial infarction, carried out cautiously and gradually in a manner similar to that described in this paper is not attended by increased risk. Furthermore, there are definite psychologic, physical, and economic benefits to be gained by avoiding unnecessary weeks of inactivity.

It has been estimated by Wright, Marple, and Beck[17] that nearly a million myocardial infarctions occur every year in the United States. Using the conservative figure of 15 per cent to estimate the proportion of "mild" cases, this means that about 150,000 such attacks occur annually. If each patient suffering a "mild" infarction is treated in the conventional fashion, he is forbidden to resume work for periods varying from four to eight weeks after the attack. A reasonable average period.

of nonproductivity would seem to be about six weeks or 42 days. This is at least 21 days longer than suggested by our method of management in "mild" cases. The economic loss represented by this unnecessary delay in resumption of productive activity is enormous—3,150,000 man-days of work. To this loss must be added the huge cost of hospitalization, the loss to the nation of goods and services and other less obvious costs such as higher sickness-insurance charges. To these purely economic losses of many millions of dollars must be added the intangible but tremendous emotional and psychologic expenditures due to worry and anxiety occasioned by enforced inactivity. Thus the annual national loss resulting from unnecessary restrictions imposed on "mild" cases of myocardial infarction is clearly tremendous.

It is to be expected that any proposal to depart from the conventional method of treatment of myocardial infarction may arouse anxiety in the patient and more particularly in his family. The lay public is well aware of the usual form of treatment of heart attacks. If it appears that the patient or his family will be apprehensive about short-term treatment, it will usually be wiser to use conventional methods. It is not suggested that at present the usual method of management should be modified in "moderate" or "severe" cases. But in the future, it should be possible to re-evaluate our handling of even these cases, especially with reference to their need for prolonged immobilization.

It will be especially difficult for young physicans to introduce a new method in the treatment of a disease as important as myocardial infarction. It is the function of those with more prestige such as the Chiefs of Medicine to cautiously and by slow stages modify traditional practice.

Summary

(1) For many decades the treatment of acute myocardial infarction has routinely included many weeks of rest, regardless of the severity of the attack.

(2) Modern technics made it possible to classify most cases of acute myocardial infarction into three categories—"mild," "moderate," and "severe." Some cases are unclassifiable since there is no sharp line of demarcation between these groups.

(3) In the typical "mild" case, the patient is young or middle-aged, usually has pain of short duration and looks and feels well 24 to 48 hours after the attack. There is no associated hypertension or previous heart disease. Fever is slight or absent. Leukocytosis is mild and transaminase levels only slightly elevated. Shock, heart failure, gallop rhythm, cardiac enlargement and other serious phenomena do not occur in these cases.

(4) In our series of 200 cases of acute myocardial infarction, the "mild" cases constituted 15 per cent of the total number but it is believed that this is a falsely low figure.

(5) A review of 400 cases of fatal acute myocardial infarction observed over a six and one-half year period, failed to reveal any patient with a "mild" case who died during or soon after the attack. The immediate mortality rate in "mild" cases must be extremely low. Certainly, it is much less than the average in all myocardial infarctions.

(6) It is absolutely necessary to take into account the complete clinical picture, including all available laboratory data, in order to diagnose and properly classify cases of acute myocardial infarction. Although the electrocardiogram is usually of great assistance in the diagnosis of myocardial infarction, the physician should be familiar with its limitations.

(7) A method of management of "mild" cases is described in which gradually increasing activity is permitted after two weeks of rest and observation.

(8) Twenty-two cases have been successfully treated in this manner. Seven cases successfully treated with less than the usual long-term period of rest have been followed for over a year. No untoward effects were observed in any of these patients. Definite psychologic and financial benefits were apparent in all. One of these patients remained ambulatory after his first infarction but survived 29 years.

(9) Clinical evidence is presented which indicates that the danger of cardiac rupture or aneurysm formation in cases of mild myocardial

infarction is minimal. This conclusion is supported by the finding that it is virtually impossible to rupture small infarcted areas in dogs two weeks after coronary ligation.

(10) In view of the very low mortality and paucity of complications in "mild" cases, it seems neither necessary nor desirable to subject such patients to the same rigorous and prolonged treatment required for more severe cases. Furthermore, early activation of these patients results in distinct physical, psychologic and financial benefits.

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Coronary Artery Disease

A Report to William Harvey 300 Years Later*

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THE HARVEY Tercentenary Congress was held in London, June 3 to 7, 1957. The American representatives on this program were F. A. Willius, J. F. Fulton, L. N. Katz, Claude S. Beck, Donald E. Gregg, Andre Cournand, Seymour S. Kety, and Stanley E. Bradley. The presentations concerned the circulation in various parts of the body. A thousand scientists from 16 different countries attended the meeting. At the close of the Congress, the writer was requested to make some remarks. The following remarks were made:

"The presentations made at this Congress may be regarded as comprising progress reports to the great master, William Harvey. Were he here to receive these reports, he would accept the new developments with the simple words 'well done.' He would give encouragement to that work which is controversial because, he, himself, knew controversy. America was a wilderness when William Harvey lived. The American Civil War was raging when Lister wrote his papers. American medicine of that time could only satisfy the requirements of a rugged existence. Modern medicine, as we know it today, is only six or seven decades old in our country. America recognizes the father-son relationship between Britain and America and extends her greetings and deep respect for the great contributions which have come from Britain."[1]

The Harvey Tercentenary may be regarded as marking the birth of THE AMERICAN JOURNAL OF CARDIOLOGY. This is a propitious date. Our research laboratories in America are busy. Large numbers of our medical personnel are being trained in research methods. New facts are being discovered. Surgery of the heart is here. Coronary artery disease is being considered from a new physiology. In reference to surgical operation for this disease, The British *Lancet* stated editorially:[2] "There is a good case for giving the operation an extensive trial, and results so far offer grounds for sober optimism." In another hundred years atherosclerosis will be better understood and it may be prevented. There will be much that is new, exciting, and important for this JOURNAL to record. If William Harvey were to write in this first issue of this JOURNAL, he would wish it "bon voyage" for its first three hundred years, 1957–2257. And who of our present generation will be remembered so long from now?

CONCERNING CORONARY ARTERY DISEASE AND SURGICAL OPERATION

The writer stated that it was an honor to be chairman of the session on the coronary circulation—a subject secondary in importance only to the circulation through the chambers of the heart itself. In order to improve the circulation in the heart's substance, it is necessary first to understand the normal. In order to help the crippled circulation, facts must be established which can be transferred and applied to both the normal and abnormal circulations. Our work has this common denominator in that it is applicable to both conditions. A new physiology was thereby developed. Some of this physiology, because it appears new and unfamiliar, has met with opposition and resistance, but that is the way with almost every new turn in medicine. Anything that breaks with custom is wrong. It was wrong to say that the earth was round when everyone knew it was flat. It is wrong to try to change the coronary artery

* Presented at the Harvey Tercentenary Congress, London, June 3–7, 1957.

circulation when everyone knows or thinks he knows that this cannot be done. It is stated that new surgical treatments for the disease have come and gone, and it is implied that this operation also is transitory. The scientist, however, knows that this work has a solid foundation in well-controlled experimentation. He accepts the axiom of occlusion, the two sequelae of occlusion, the theory of oxygen differentials, and the importance of an even distribution of blood. He accepts these elementary considerations and wonders why these concepts were not brought to light long ago. Furthermore, the scientist will not be disturbed by the fact that 100 consecutive patients with coronary artery disease were operated upon and the operative mortality was zero. He will be pleased with the clinical results, and he will consider surgical operation as the most desirable treatment for the disease.

A brief résumé of the Harvey presentation follows:

Axiom of the Disease

When a coronary artery is occluded or narrowed, the fate of the patient depends upon the amount of blood in the ischemic muscle distal to the occlusion or stenosis. Additional blood to the ischemic muscle is helpful and further reduction in the amount of blood to the ischemic muscle has the opposite effect. This is the axiom of the disease and it is elementary information. It is the key to effective treatment. The scientist readily accepts these statements.

How Much Blood Is Necessary for Protection?

This subject has been investigated in our experimental laboratory, and my former associates, Mautz and Gregg, contributed a method which made it possible to measure the amount of blood in the arterial system distal to the occlusion. The circumflex artery is ligated at its origin. The amount of blood available to the muscle, which was made ischemic by this ligature, now comes from adjacent muscle by way of intercoronary communications. The axiom of occlusion applies here. The amount of blood in normal dogs varies from less than 1 cc/min to 8 tc 10 cc/min and to even larger amounts, although this is rare. The average amount in a large number of normal dogs was 3.8 cc/min. This amount was determined by cutting the artery distal to the occlusion and measuring the amount that ran out of the artery. When this blood was allowed to escape so that it was no longer available to the muscle, the electrical condition of the heart immediately deteriorated and in a few minutes the heart fibrillated (Fig. 1). The statement can be made that quantities of blood within the range of several cubic centimeters per minute can affect the electric condition of the heart when a major artery is occluded.

We found by experiment that 5 cc/min, 300 cc/hour, saves the life of the dog when the descending ramus of the left coronary artery is ligated in one step at its origin and 6.5 cc/min or 390 cc/hour saves life when the circumflex ramus is ligated. When these quantities are present, the currents within the muscle after arterial occlusion are not strong enough to reach the fibrillation threshold but these quantities are not adequate to prevent infarction. There may be no gross infarct but under the microscope fibrosis is present. To the scientist this approach to the coronary problem and these measurements are fundamental. The axiom of the disease is nothing less than the scientific starting point for all approaches to understanding and treating the disease.

Two Sequelae of the Disease

Stenosis or occlusion carries two distinct sequelae. One concerns differences in oxygen content of muscle and the other concerns inadequate inflow of blood. Differences in oxygenation of muscle produce electric instability, anginal pain, and currents that may be strong enough to fibrillate the heart and kill. Reduction of inflow produces death of muscle and infarction. These two reactions should be separated; otherwise they produce confusion. Examples of confusion are seen in the title of round table conferences where myocardial infarction is the subject for discussion. In these conferences, the discussion is not confined to infarction. It takes in something else which is ill defined and poorly understood. This deficit

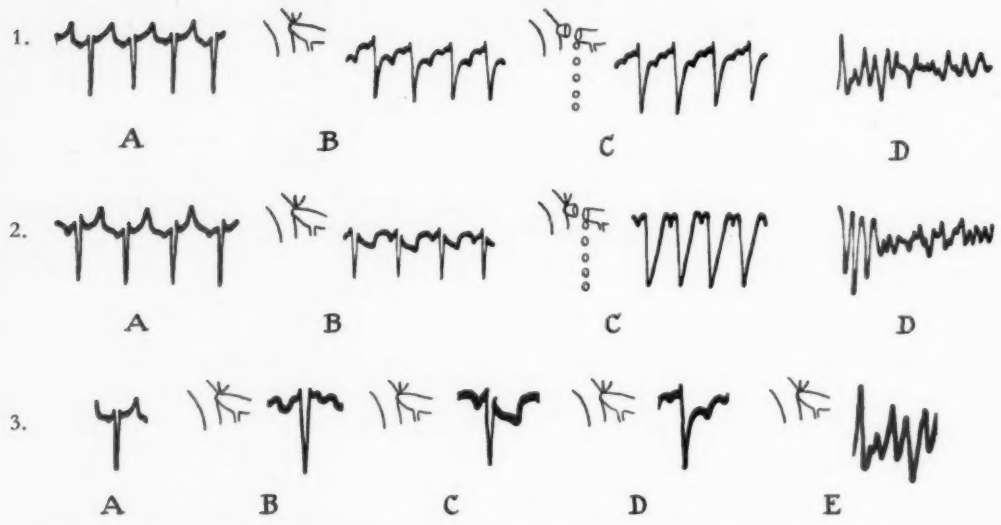

Fig. 1. Electrocardiograms, dogs, before and after ligation of circumflex ramus of left coronary artery at its origin. The amount of blood distal to the occlusion determines the fate of the experimental dog and also the fate of the human with the disease. This is an axiom in coronary occlusion. The amount of blood in this ischemic muscle varies. 1-A is normal; B is after the artery is occluded, moderate S-T depression, measured amount of blood distal to occlusion, 2.4 ml/ min, 144 ml/hour; C, this blood is allowed to escape by cutting the artery distal to the ligature and the artery bleeds to the air, severe S-T depression; D, the artery bleeds 4 min when the heart fibrillates. Fibrillation signifies death. This quantity of blood, small as it may appear, is important for the heart.

2-A is normal; B is after the artery is occluded, slight S-T depression, measured amount of blood distal to occlusion, 6.8 ml/min, 408 ml/hour; C, this blood is allowed to escape, severe S-T depression; D, the artery bleeds 6 min when the heart fibrillates. In 2-B the amount of blood in the ischemic muscle is 4.4 ml/min more than in 1-B (6.8 minus 2.4), and S-T depression is less.

3-A is normal; B, C, D, and E are after occlusion of artery. In B there were 10 ml/min, 600 ml/hour available, slight widening of QRS; in C there were 6 ml/min, 360 ml/hour available, slight S-T depression and widening of QRS; in D there were 4 ml/min, 240 ml/hour available, marked S-T depression; in E there were 2 ml/min, 120 ml/hour available and the heart fibrillated. Surgical operation increases blood supply to ischemic muscle in quantities represented in these experiments.

From: Beck, Claude S.: *Ann. Surg.* J. B. Lippincott Co., Philadelphia, 145: 440, 1957.

in the science is also shown when a mild coronary occlusion is defined. The various clinical manifestations are mild but something which was not mild killed the patient. It is scarcely known that there is little or no obligate relationship between muscle mass killed and the electric currents produced. The scientist considers this separation as an elementary requirement in understanding the disease.

The Stable Heart[3] (Fig. 2*)

A uniformly well oxygenated (pink) heart is electrically stable. A uniformly cyanosed (blue) heart is electrically stable. The stability of these hearts can be readily shown in the laboratory where electrograms are taken from the surface of these hearts. The electrograms in each are precisely similar. Cyanosis is produced by clamping the intratracheal tube in the anesthetized dog. The entire dog becomes cyanosed and so does the heart. After the tube has been clamped for six to nine minutes, the heart becomes deeply cyanosed; it dilates. The beat becomes weak. It stops in standstill. It does not fibrillate. According to these experiments, the amount of oxygenated blood delivered to the heart has no relationship to the production of electric currents in the heart. The factual nature of this statement cannot be disputed. The degree of cyanosis or lack of

* Fig. 2: From Beck, C. S., and Leighninger, D. S.: *J. A. M. A.* 159: 1264, 1955.

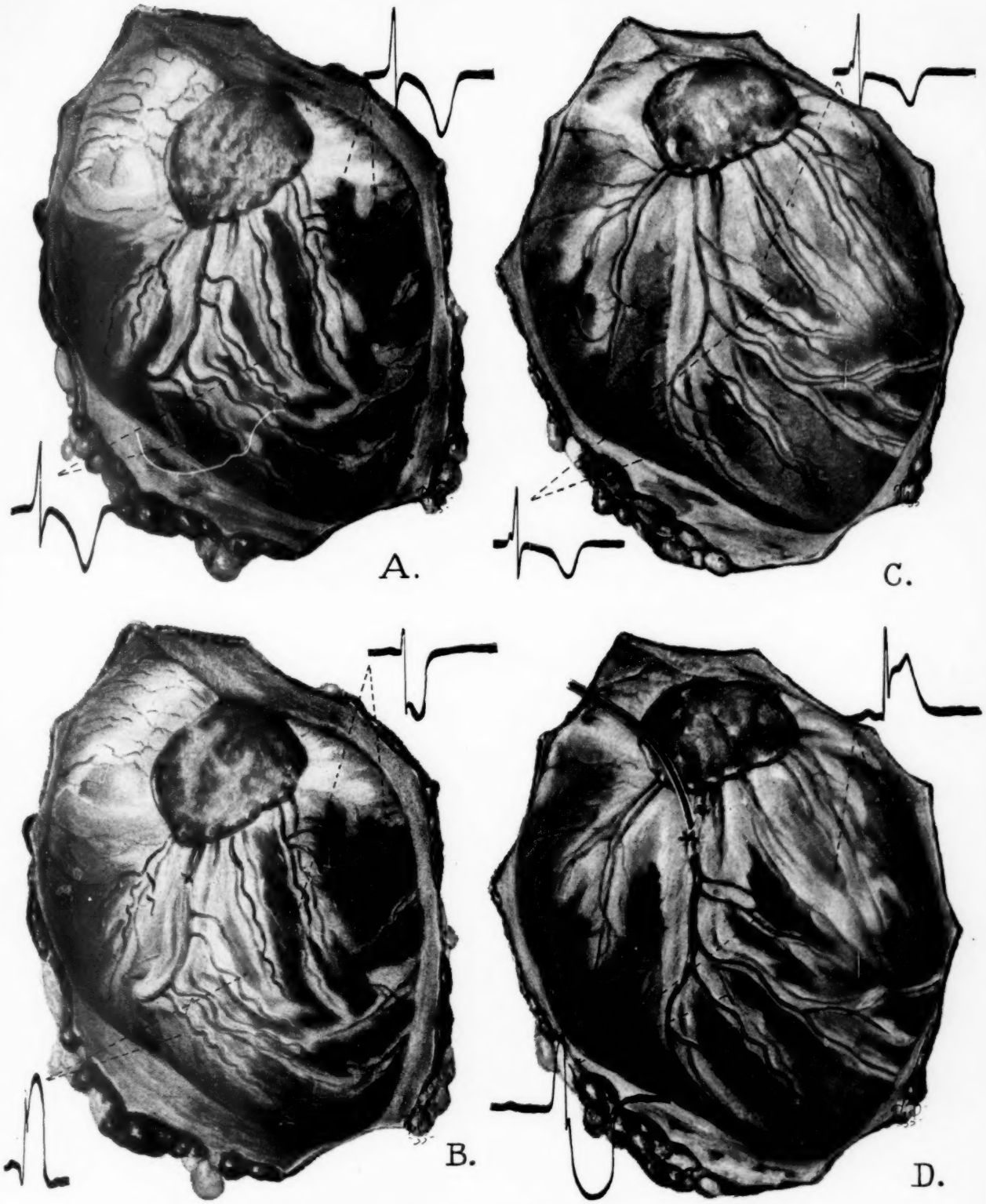

Fig. 2.—Dog hearts illustrating four conditions of myocardial oxygenation, with direct epicardial electrocardiograms demonstrating measurement of electrical potentials. *A* and *C* are the same heart; the one is uniformly well oxygenated, and the other is uniformly and severely cyanosed. These hearts are electrically stable as shown by the isoelectric S-T segment in each condition. *B* and *D* are electrically unstable because the oxygen tension in each heart is not uniform throughout. The S-T segment is depressed over the pink or well-oxygenated myocardium and elevated over the blue or cyanosed myocardium. These differences in potentials are often strong enough to fibrillate the heart. The term "current of oxygen-differentials" is introduced to replace "current of injury," which is obviously incorrect. A uniformly cyanosed heart is not an injured heart.

oxygenation must be uniform. It is the same everywhere in the heart muscle. This requirement should be emphasized.

This fact has far reaching clinical application. If coronary inflow is reduced uniformly, the heart does not fibrillate nor does it produce anginal pain. A cyanosed heart is not painful. A blue baby does not have angina pectoris, but a child with one artery coming off the pulmonary artery and the other coming off the aorta does have anginal pain and this heart is likely to fibrillate. This elementary physiology places emphasis upon uniformity of distribution as one factor in the coronary problem as contrasted to total inflow through the coronary arteries as a different factor. These two factors considered separately will help to clarify the physiology of the coronary circulation.

Another aspect of the problem concerns the amount of inflow necessary to maintain the heart beat, when the anatomy of the coronary arteries is such that a red cell can go anywhere equally well within the heart's substance. Under this condition, how much blood is necessary to preserve the heart beat? We found that an inflow through a stoma of 1 to 1.5 mm was sufficient to maintain normal activity of dogs. All coronary inflow was occluded except for an opening of this size in one of the arteries. These experiments have their counterpart in patients with occlusive or severely stenosing disease. Reduction in lumina of the arteries may be so severe that one wonders how the heart gets enough blood to support its beat. The hemodynamics of the coronary circulation are such that considerable quantities can flow through severe stenosis. The total coronary artery inflow in a dog of medium size is about 100 cc/min. The circumflex ramus of the left coronary artery carries almost half of this amount. The amount of blood that flows through an opening 1.5 mm in diameter with a pressure of 100 mm Hg on one side and 20 mm Hg (capillary pressure) on the other side is 315 cc/min; the flow through an opening 1 mm in diameter under the same conditions is 140 cc/min. According to these figures sufficient blood to support the heart beat can enter the heart in the presence of severe stenosis. This information places emphasis upon distribution of this blood. An uneven distribution and not an inadequate inflow kills most of those who die from the disease. The heart resists the entrance of outside blood but much can be done to make a more even distribution of this blood. In most instances of the disease, and in most of the humans who die from the disease, the heart does not need additional blood. It needs an even distribution. Many human hearts give silent testimony of this fact (Fig. 3).

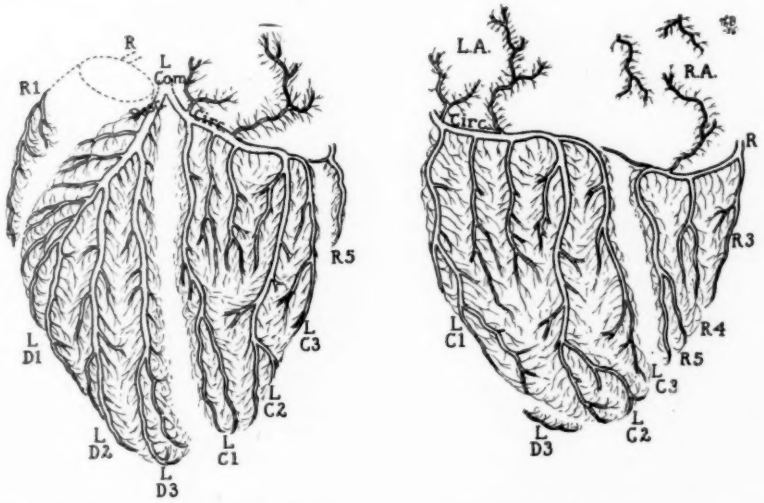

Fig. 3. Segmental anatomy, coronary arteries; D1, 2, 3—branches of anterior descending artery; C1, 2, 3—branches of left circumflex artery; R1, 3, 4, 5—branches of right coronary artery. Differences in blood supply between segments → instability → fibrillation. Reduction → infarction. Connections between segments → protection.

The Disease Versus Intercoronaries

Data from Zoll, Wessler, and Schlesinger[3] obtained by a study of human hearts show (1) that 9 per cent of normal hearts possess intercoronaries, (2) that this incidence does not change until stenosis exceeds 75 per cent of the diameter of the artery, (3) that the incidence rises to 58 per cent when the narrowing is between $^3/_4$ of the diameter up to but not including occlusion, (4) that the incidence is 89 per cent when the narrowing becomes acute occlusion and (5) the incidence is 100 per cent when narrowing becomes complete and chronic occlusion. My comment on these data is as follows: Humans with normal coronary arteries were probably born with intercoronaries—9 per cent have them, 91 per cent do not have them. Those humans with them are in a protected position if narrowing or occlusion should develop. Stenosis up to three-fourths of the diameter is not effective in producing them and from three-fourths up to but not including complete blockage, the response with intercoronaries is not nearly adequate because so many humans die with stenosis of these degrees. That every human heart with chronic occlusion has intercoronaries is open to two interpretations: (1) occlusion produced them, and (2) the fact that intercoronaries were always present indicates that they were essential, otherwise the heart could not continue to beat so that the disease could become chronic. These humans probably were the 9 per cent who were born with intercoronaries and those without them died. If the heart possesses some intercoronaries then it is in a favorable position to continue to beat as the stenosing disease increases and if the heart can go through the crisis of occlusion, then an excellent set of intercoronaries develops. Occlusion is an excellent stimulus for intercoronaries provided those that fell by the wayside as the stenosing process became more severe are not taken into consideration. The patient with clinical evidence of coronary artery disease has a precariously balanced circulation in which small alterations produce important consequences. It would be desirable if the other 91 per cent of the humans had intercoronaries for protection.

The Unstable Heart[4] (Fig. 2)

An electric current is produced when pink or well oxygenated muscle is in contact with blue or cyanosed muscle. These differences in oxygenation are produced by ligature of a coronary artery in a pink or well oxygenated heart and by perfusing well oxygenated blood into a coronary artery of a cyanosed heart. The first experiment produces an area of cyanosed muscle in juxtaposition to well oxygenated muscle. The second experiment reverses the oxygenation. An electrogram from the surface of these hearts shows a depressed S-T segment over the pink or oxygenated muscle and an elevated S-T segment over the blue or cyanosed muscle. These hearts are electrically unstable and the current generated within the muscle and at the plane of contact is often strong enough to fibrillate the heart as if the heart were touched by an electric wire. The physiologist labeled the current obtained after coronary artery occlusion as "current of injury." This obviously is not correct and should be replaced by the term "current of oxygen differentials." A cyanosed heart is not an injured heart because it is cyanosed. These experiments indicate that an uneven or "checkerboard" distribution of oxygenated blood produces electric currents. These currents are responsible for the death of the vast majority of those who die from the disease. The scientist considers the facts concerning (1) total inflow versus degree of stenosis, and (2) an even distribution of the blood that is available, as elementary concepts of the disease. He wonders why they have not been brought to light long ago and he cannot understand why they are not readily understood and accepted. Perhaps the electrocardiogram and complacency of attitude have displaced a critical attitude which makes for progress.

Two Types of Death

According to the physiology so far presented, there should be two types of deaths produced by the disease. There are two types of death produced by the disease. One is due to the fibrillating currents that destroy the heart beat; this is the fatal heart attack. The other is due either to inadequate inflow of blood or to muscle

destruction occurring in the absence of fibrillating currents. The heart goes into failure or it simply stops beating in standstill. Perhaps this is oversimplification but it serves a purpose in distinguishing death due to a fatal heart attack from death by myocardial failure or inadequate inflow. A third type of death occurs in the absence of severe muscle damage without severe inflow reduction and without fibrillation. The heart simply fails to convert its energy substances into mechanical energy. This is a problem for the biochemist and the physiologist.

It is obvious that these two conditions require different types of treatment. The patient with severe muscle destruction requires the treatment for cardiac failure. The patient with or without anginal pain, whose life is threatened by a fatal current, requires a different type of treatment. This patient needs reduction of the current so that it will not kill and if treatment reduces the current it also reduces the anginal pain. Our discussion henceforth will concern this second condition. Damage to muscle and arteries inflicted by the disease is not reversible. Restitution is not possible.

The Death Factor

The scientist wants to know more about the death factor in humans who have a fatal heart attack. Is it an avalanche of destruction in the heart which by virtue of its enormity is beyond help, or is it a mysterious evil which defies understanding? Will the profession for all time remain critical and resist doing anything about the death factor? There is considerable information about this factor. It appears with or without warning. It is an electric current and it is produced within the heart by oxygen differentials. It can be prevented by reduction of these differentials and it can be made to disappear after it kills. It appeared in two patients with coronary artery disease; it fibrillated the heart; and the author successfully defibrillated the heart. Each of these patients is living. It has been made to disappear in several other patients by other surgeons. These experiences so far have been few but the attempts have also been few. The conclusion is that the death factor may be a small factor, comparable to stopping and starting the pendulum of a clock or turning the ignition in a motor. It is preventable as shown in our laboratory and sometimes it is reversible. These statements of facts give hope for future progress.

What Can Be Done?

The blood that enters the diseased coronary arteries can be distributed by surgical operation so that it accomplishes its greatest amount of good. The Beck operation produces an inflammatory reaction on the surface of the heart which in turn produces or opens up intercoronary arterial channels. The operation rarely adds new blood to the heart from outside sources. It redistributes its own blood so that the heart can enjoy a "balanced circulation." The beneficial effect of an even distribution is obvious to the scientist (Fig. 4).

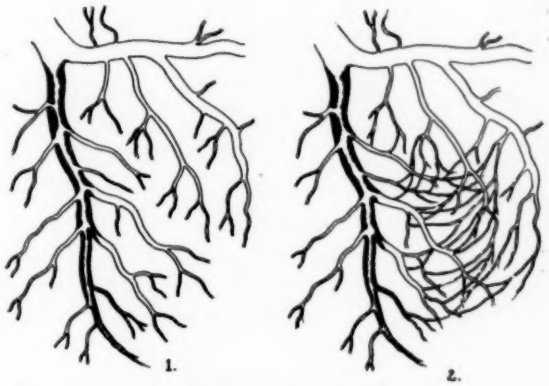

Fig. 4. Artist's sketches of the left coronary artery and its two branches. (1) The descending ramus is stenosed throughout its entire extent. This produces an uneven distribution and electric currents. This type of condition often kills on the golf course. The stenosis is not severe enough to tap blood from the circumflex muscle where the blood supply is more than adequate. (2) Operation taps the circumflex bed by production of intercoronaries and these produce an even distribution.

Almost all avenues of approach to improve the crippled coronary circulation have been investigated by the writer and his associates.[4–6] The scientific approach to a disease that kills and incapacitates so many people requires thorough investigation of every conceivable angle in order to establish the most effective form of treatment. We have performed some 6,000 experimental operations. We conducted many unrewarding experiments. But now we

are on an even keel, and the problems have become simplified. We know that the heart resists blood from outside sources and while it is not impossible to produce extracoronary anastomoses between heart and grafts, they cannot be produced with any degree of regularity. We know that red blood delivered to the capillary bed from the venous side of the circulation enters the capillaries for several months but later on these avenues are cut off by intimal thickening of veins but interestingly enough this procedure provides an excellent set of intercoronary arterial channels. But this is a difficult way to produce these channels and we are using more simple methods.

The scientist emphasizes any and all physiologic methods for improving the crippled circulation and he de-emphasizes the modifications in technic merely for the sake of change. He demands to know what any procedure can do physiologically before it is applied to the human. Furthermore, he wants it tested and measured before it is applied but after this has been accomplished, and it has been shown to be beneficial, then acceptance, application, and evaluation of the procedure on patients are in order.

The author's operation consists of abrasion of the lining of the parietal pericardium and epicardium, narrowing of the coronary sinus to a diameter of 3 mm, application of powdered asbestos (0.3 g) to the surface of the heart and the application of mediastinal fat as a graft to the surface of the heart. This operation increases average backflow from 228 cc/hour to 510 cc/hour, or an increase of 282 cc. For many years we have been testing various chemical agents to replace epicardial abrasion and we have not been able to find a satisfactory and effective replacement until several months ago. We found that a light application of an aqueous solution freshly made up of 5 per cent trichloracetic acid to the epicardium as a replacement for epicardial abrasion in 14 dogs gave an average backflow of 10.1 cc/min, 606 cc/hour. This is an increase of 378 cc/hour produced by the operation. This is a preliminary study only and further tests are indicated. The author has been using it on patients and in some instances has not abraded the surface of the heart. Ten cc of blood/min from the ligated and cut circumflex artery is about one-fourth of the inflow in this artery under normal conditions. This blood comes from the descending ramus and the right coronary artery and these arteries can carry much more blood than their respective capillary beds can accept.

Application to Humans

Operation cannot cure the disease. Once the muscle is destroyed and the arteries are stenosed or occluded, nothing will reverse these conditions. Nothing will prevent additional stenosis or occlusion in the future. It is possible for a patient to get a good result from operation and then die later on from progressive disease. These are the facts as they now exist and when recognized the positive accomplishments of operation can be appreciated. If the limitations are not recognized then it is not possible to recognize the potential benefits of operation.

The most favorable type of patient for operation is the one who has minimal arterial and myocardial damage. One need scarcely answer the question as to what can be accomplished when arterial inflow is almost completely shut off or when the muscle is so extensively damaged that the heart fails. It is obvious that little can be accomplished in these conditions. Many patients request operation because of angina pectoris, cardiac failure and weakness. Operation is scarcely beneficial for these patients and the risk of operation is high. The ideal patient for operation is one with pain and little damage in the heart. Such a patient can be cured of pain and with almost normal anatomy the patient has a good prognosis. Should a member of a "coronary family" be operated upon as a prophylactic measure? This query usually arouses adverse criticism but in defense of this idea are these considerations (1) it will give the heart a protective set of intercoronary channels; (2) the operation will be done when the risk of the procedure is almost zero; (3) the period of hospitalization is short and the postoperative period is not an ordeal. These considerations may not apply later on when it is too late. The likelihood exists that every male member of a coronary family will

develop coronary artery disease and it is reasonable to protect him by operation before the disease develops. It is probable that members of coronary families possess little or no intercoronary protection.

The indications for operation include patients with coronary insufficiency and patients with one or more infarcts. Those with insufficiency are operated upon when the diagnosis is made; those with an infarct are given a waiting period of six months so that the healing process will have become completed. A waiting period of three months is given to patients who have had any recent progression of symptoms. Anginal pain is not a requirement for operation. Age of the patient is a factor. A patient 67 years of age without pain is not in the same category as a similar patient at 57 years, but the 67-year-old man with pain is a candidate provided his body elsewhere is in good condition. If there is a question concerning risk, it is advisable to wait three months and then decide.

Clinical Results and Mortality

Surgical operation reduces or cures anginal pain. It is the most effective treatment for pain. Many of the patients return to work. It is only necessary to talk to the patients and their families to appreciate these results. The psychologic overlay in evaluating results is appreciated by the author but this should not prevent proper appreciation of the results. Operation saves life in a dog when a coronary artery is occluded. It also saves muscle. These facts were established under well-controlled conditions and they are not to be disregarded because they were established on dogs and not on humans. It might be possible to determine on a statistical basis whether operation prolongs life or delays death in the human. An affirmative answer appears to be a good probability. A statistical analysis is about to be made, but relief of anginal pain and the protection demonstrated in the laboratory are adequate reasons for operation.

There were two operative deaths in the last 178 consecutive patients operated upon or 1.2 per cent. The mortality was three for 25 minutes because one of the patients fibrillated for this period of time and then mortality dropped back to two again after the death factor was reversed and a coordinated beat was restored. This patient is doing well several months after operation. One hundred consecutive patients were operated upon with zero operative mortality.

Conclusions

(1) A new physiology on coronary artery disease has been established.

(2) New clinical concepts of the disease are presented. These are based upon elementary considerations and provide an orderly approach to the disease.

(3) Operation makes it possible for the heart to "enjoy" a more equal distribution of the heart's own blood. Clinical results are good or excellent.

(4) One hundred consecutive patients were operated upon with zero operative mortality and in the last 178 consecutive operations the operative mortality was two or 1.2 per cent.

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Bilateral Internal Mammary Artery Ligation for Angina Pectoris*

Preliminary Clinical Considerations

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Coronary disease is increasing in spite of all efforts to check its progress. The only practical solution to the problem seems to be prevention which is a remote possibility at this time. While this solution is being pursued, physicians are attempting by both medical and surgical means to relieve the suffering caused by atherosclerosis.

Medical therapy may enable a patient to live with his diminished myocardial blood supply but, as pointed out by Beck and Brofman,[1] has never been shown to increase the available blood supply coming through the damaged arteries. Surgery, over the years, has attempted to augment or redistribute the coronary flow in order to prevent failure of myocardium, or, more important, to prevent serious arrhythmia. As the great majority of deaths from coronary disease result from cardiac mechanism breakdown rather than from muscle failure, the addition of only small quantities of blood to the supply available through the damaged arteries may be life saving.

Experimental Basis of Operation

In 1880 Ludwig Langer[2] demonstrated by injection technics anastomoses between the vasa propria (coronary system) and the vessels of neighboring organs. He went so far as to suggest that "the heart can also be nourished with blood through collateral circulation when one or both branches of the coronary arteries are made impervious as a result of an atheromatous process."

In 1936, Mautz and Beck[3] injected chronically occluded coronary arteries of the dog heart with barium sulfate gelatin mixtures (by the method of Louis Gross). Their studies demonstrated newly formed arteriolar connections between the coronary artery system and the internal mammary system. These anastomoses were large enough to permit free passage of the gelatin barium mixture. In histologic sections it was noted that this mixture passed through arterioles with difficulty or not at all if they measured less than 70 micra in diameter. This would indicate that the anastomatic vessels were of reasonable size.

These studies also demonstrated tremendous enlargement of anastomatic channels between chronically occluded coronary arterial segments and coronary arteries which were patent. These vessels had increased length. Their diameters were greatly increased (as much as 14 times) over maximum diameters of normal intercoronary anastomoses. They did not resemble arterioles as they lacked smooth muscle and elastic tissue. In a series of studies from the Beck laboratories (reported by Mautz and Gregg in 1937)[4] it was shown that following chronic occlusion of a large coronary branch a massive new collateral circulation develops. Further studies by Gregg, Thornton, and Mautz[5] showed that from two-thirds to nine-tenths of this

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anastomatic flow into a chronically occluded artery came from the unoccluded coronary arteries. The remaining one-tenth to one-third of this blood must have come from septal arteries or from extra cardiac sources. These sources could well be the internal mammary system.

In 1939, at the suggestion of Fieschi, Zoja and Cesa-Bianchi ligated the internal mammary arteries bilaterally in the second interspace in a patient who was suffering from intractable angina which followed a myocardial infarction. Two years later this patient was reported as living and comfortable. The operation was lost sight of in war years, but in 1955 it was revived by Battezzati, Tagliaferro, and De Marchi.[6,7] These authors followed 70 cases for up to 18 months and were able to report 64 of them living and improved.[8]

When we became aware of these results in Italy, a series of experiments were begun in the Cardiovascular Research Laboratories at Presbyterian Hospital in Philadelphia. The research team was able to demonstrate that dye (fluorescein mixed with Evans blue) or I^{131} solutions injected into the section of the internal mammary artery isolated by ligation at its source from the subclavian and in the second interspace rapidly passed into the coronary system. In these acute experiments the aorta, the lung hili, the vena cavae and azygous vein, and all other sources than the mediastinal branches of the internal mammary were occluded. The dye, or I^{131} as the case might be, was demonstrated in the major coronary vessels in from 30 seconds to 6 minutes time. In other experiments it was noted that pressures in the section of the internal mammary proximal to ligation in the second interspace rose 7 to 14 mm of Hg.

The details of this surgery have been reported elsewhere[9]; for this reason the operative technic will not be discussed in this paper.

Indications and Preoperative Preparation

At present the prime indication for operation is angina pectoris due to atheromatous coronary disease or to aortic valvular disease. We have noted benefit in a few patients who have not had true angina but whose coronary insufficiency was noted by bouts of paroxysmal pulmonary edema or paroxysms of serious arrhythmias.

The diagnosis of angina pectoris is usually an easy one to make and in about three-fourths to four-fifths of cases can be corroborated by objective studies such as the electrocardiogram (with or without an exercise test). However, in about one-fifth of the cases it is not possible to find any objective test which is abnormal. In these cases the "Standardized Exercise Test" described by Riseman is of great value.[10] A careful history is still the best diagnostic method available.

We do not feel that it is advisable to perform this surgery on patients who are not convalescent at least three weeks to a month following a previous infarction and our immediate failures are confined to this type of patient and to the patient who is having symptoms of impending infarction. Such cases should be treated medically until some stabilization of symptoms and electrocardiographic changes is demonstrable.

It is not a good idea to keep a nervous patient with angina pectoris in the hospital for a long period while one proceeds with a complete check up including x-rays of the gastrointestinal tract and gall bladder. These studies are best done before admission to a hospital to minimize the nervous reaction which might well precipitate an infarction. This nervous tension is a dangerous thing. Two of our patients developed pain while on a litter going to the operating room. One was operated on, went into ventricular tachycardia, and died in spite of heroic therapy including massage. The other was returned to his room and treated for a fresh myocardial infarction. He survived and as his angina has not returned since the infarction, no surgery is now contemplated.

In view of the fact that the risk of this operation is essentially the risk of anesthesia, one must be concerned about the type of anesthetic, the mode of administration, and the skill of the anesthetist. In those patients whose infarction is recent (within three weeks to one month), or in those whose infarction seems impending, a local anesthetic is used. One side is injected with 0.5 per cent procaine and operated. Then the other side is done. This method tends to prevent a sudden lowering of blood pressure by large quantities of procaine. It has not been

TABLE I

Results of Bilateral Ligation of the Internal Mammary Arteries

50 patients followed for a period of 2 to 6 months

	Total group	44 patients under 70 years
Improved		
Asymptomatic	18	18
Moderate	11 (34 or 68%)	11 (32 or 64%)
Slight	5	3
Clinically unchanged	11 or 22%	9 or 18%
Dead		
Within one month	3 (5 or 10%)	3 or 6%
Over one month	2	

necessary to use more than 50 cc of solution if the injection is made properly.

In those patients who are stable, or in those whose nervous state militates against a local anesthetic, a light general anesthesia induced by sodium pentothal and maintained on 50 per cent N_2O and O_2 has been used. Small amounts of succinyl choline may be used as a supplement. Endotracheal intubation has not been necessary but should be available. At the present time we have not had a fatality in cases where local anesthesia has been used. We are beginning to feel that this is the method of choice.

Results

Eighty-two patients have been operated on to date. The criterion for surgery was the presence of angina pectoris. In this group no patient was turned down for surgery because of age, debility, unstable disease, hypertension, enlarged heart or the like, except one patient previously mentioned who was not done after he had an infarction in the operating room prior to anesthesia. These cases were not "selected" and many would fall into a "salvage" classification. The age range was from 33 to 82 years.

Fifty of these patients have been carefully followed for from one to six months and from this group the following analysis is made (Table I).

Thirty-four patients (or 68 per cent) have been clinically improved in that they have no angina (18 patients—36 per cent) or that they now have fewer and less severe attacks of pain (16 patients—32 per cent). In most of these, improvement or abolition of preoperative pain and discomfort was immediate. In some this relief came later, as long as a week or two before the result was complete.

In 11 patients (22 per cent) no improvement has been apparent. Five patients have died since surgery. Of five patients who were operated upon within two weeks of an acute infarction, three are now dead.

Although the total cases are far too few for real conclusions to be drawn, it appears that the moderately hypertensive patient obtained the better result (Table II). It may be that the hypertension produced a more marked gradient of pressure from the internal mammary through the pericardiacophrenic artery to the vessels of

TABLE II

Results According to Basic Pathologic Pattern

	Arterio-sclerosis	Hyper-tension	Hemodynamic	
			Aortic stenosis	Aortic insuf-ficiency
Total	40	7	2	1
Asymptomatic	12	3	2	1
Moderate improvement	9 (26 or 65%)	2 (5 (71%))	0	0
Slight improvement	5	0	0	0
Clinically unchanged	9	2	0	0
Dead	5	0	0	0

the myocardium. This is an inference and has no definite proof as yet.

The correlation of the number and type of preceding infarctions to the clinical results is interesting. The 45 living patients suffered a total of 46 infarctions or about one per patient. The five patients who died averaged more than two infarctions each and four of them had had infarctions involving the septal area. Patients who have had septal infarctions seem less likely to benefit from this surgery and are greater operative risks.

Of the 50 patients whose tracings could be repeated over periods of one to six months postoperatively, 13 had electrocardiographic evidences of improvement and 9 had improved ballistocardiograms. Only one patient showed improvement in both electrocardiographic and ballistocardiographic patterns. Although 68 per cent of the patients showed clinical improvement, only 42 per cent have shown objective evidence of improvement. It might be well to note here that only 20 patients have had ballistocardiographic readings taken over one month from the time of surgery. It is usual for the ballistocardiogram to deteriorate in the first week after any surgical procedure and these patients left the hospital about one week after surgery. As more ballistocardiographic data are obtained at longer intervals after surgery, this situation may change. It would be of interest here to point out that all our ballistocardiograms are taken on the Starr type table and Dr. Isaac Starr has been kind enough to read all these tracings for us.

Not only was benefit apparent in relief of anginal pain, but also in relief of the distress in one case of severe shoulder-hand syndrome. This man also had severe angina and now feels he is improved moderately from his angina as well. In one case of ventricular paroxysmal tachycardia which occurred in bouts several times a week prior to surgery, the patient has had but one attack which was easily controlled since his operation.

Another patient, whose coronary insufficiency was expressed in paroxysmal pulmonary edema and who had been unable to sleep recumbent in bed for two years, now has less severe attacks and since operation sleeps in bed with the aid of two pillows. These two cases, not having angina, are not included in the 50 cases analyzed above.

There are still many physicians who seem unable to realize that functional improvement in coronary artery disease is not always demonstrable by objective measurement. Perhaps no disease except mental illness is so resistant to objective testing as is angina pectoris. We believe that when the patient feels better, is able to return to productive occupations, and lives a more normal life, he is improved. There is no machine available today to document these improvements other than the old-fashioned history of the case. In the evaluation of coronary disease, especially the anginal phase of coronary disease, time is the only measure which will give true answers. It is evident to us that evaluation of this surgical procedure will have to be based on a formula involving large numbers of patients and much time leavened by careful follow-up and history taking.

Summary

Since December of 1956, 82 patients have been operated upon. The criteria for ligation of the internal mammary artery in the second interspace, was the presence of angina pectoris. No other factor except this was used in selecting these cases. Fifty of the cases have been followed for two to six months. When the report is made up of this group of fifty, it can be noted that eighteen are asymptomatic, eleven are moderately improved, five are slightly improved, eleven are unchanged. Three of the patients died within one month of surgery, two patients died more than a month after surgery. In dividing the cases up into basic pathologic patterns, it was noted that those with hypertension as well as coronary disease seemed to do quite well. The hemodynamic types which accompanied valvular disease were also benefited, although these groups were not large and made up only ten of the fifty. Of the five patients who were operated upon within two weeks of an acute infarction, three are now dead. One death occurred in a patient with lymphoma; another death occurred in a patient who had pyelonephritis and developed uremia. It is pointed out that local anesthesia seems to be

safer than even light general anesthesia for this procedure. It is also evident that evaluation of this surgical procedure will have to be based on a formula involving large numbers of patients and much time, leavened by careful follow-up studies.

Addendum

Since the submission of this paper for publication, an additional 53 cases have been done, bringing the total to 135 cases. In evaluating the results of the first 100 patients, we find no significant changes in the statistical results reported in this paper.

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Aggravation of Mitral Heart Disease Following Pregnancy

A Statistical Study of 233 Cases

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RECENT STUDIES[1,2,8,13,15] indicate that most patients with rheumatic heart disease tolerate pregnancy satisfactorily with but a low incidence of functional deterioration and only rarely with episodes of acute failure. A brief review of our clinical material appeared to support these findings but at the same time appeared to challenge the general concept that aggravation of the rheumatic process by pregnancy occurs only in the period of gestation. Cases were observed in which deterioration of the cardiac status took place in the weeks or months following delivery or even following a miscarriage.

The therapeutic implication of this initial survey indicated a need for a more detailed evaluation. The present report is based on a statistical analysis of 233 patients with mitral disease complicated by at least one pregnancy. Any patients whose cardiac condition deteriorated during pregnancy were not included in the series.

MATERIAL AND RESULTS

Data Based on the Number of Pregnancies: There were 500 personally documented pregnancies among the 233 patients with mitral valve disease. Included in this group were patients with as many as four pregnancies.[12]

Gestation appeared to have no effect on the course of the underlying heart disease in 217 or 43.4 per cent of the total of 500 pregnancies. The remaining 283 pregnancies (56.6 per cent) were complicated by arthralgias, reactivation of the rheumatic process or by frank aggravation of the heart disease. In this latter group complications appeared in 160 instances during the first year following delivery and in the remaining 123 at a later date.

Data Based on the Number of Patients: When the data were analyzed according to the number of patients, it was noted that the course of the cardiopathy was uninfluenced by the pregnancy in 101 patients (43.3 per cent), and was made worse in the remaining 132 patients (56.6 per cent). In 39 of these patients the period of aggravation occurred more than a year following delivery. These cases were accordingly discarded from further analysis. Thus there remained 93 patients suitable for study of the details of the aggravation. This consisted of combined polyarticular rheumatism and cardiac dysfunction in 29 patients and cardiovascular symptoms solely in 64 patients.

Among the semiological features which characterize the successive periods of cardiac deterioration it is possible to analyze only those functional complications which are described more or less accurately by the patients themselves. The documentation of such evidence is significant since stethacoustic, electrocardiographic, radiographic and laboratory data generally confirm the clinical impression of aggravation concluded from the patient's complaints.

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The patient's story is of further importance since it is unusual for the same clinician to be in a position to follow personally the same rheumatic patient through several decades of her life. Our records indicate that the analysis of the patient's functional difficulty (primarily dyspnea and diminished exercise tolerance) affords a solid basis of classification of the degree of cardiac deterioration. We have therefore classified our patients according to the criteria as set forth by the American Heart Association.

COMPARISON OF CARDIAC STATUS BEFORE, DURING, AND AFTER PREGNANCY.

All cases were analyzed by considering the time when cardiac deterioration developed in relation to time of parturition. Noteworthy is the fact that no instance of aggravation developed in the first 12 days postpartum, during which time all patients were followed closely in a maternity hospital.

After discharge all patients were examined at regular intervals during the first year following parturition by the cardiologist. Interestingly it was found that of the 93 cases, a significant majority, 68 cases, evidenced a decrease in their functional classification during the first six months and 25 cases in the last six months. Figure 1 illustrates the observations based on a comparison of the functional status of the patient before pregnancy and during the postpartum period when increased cardiac disability developed.

(1) *Women with Mitral Disease (Class I) before Pregnancy (48 patients):* (a) Cardiac aggravation occurred during the first six months after parturition in 39 patients:

Nine patients remained in Class I but developed reactivation of rheumatic fever.

Two patients remained in Class I but later developed progressive asthenia.

Thirteen patients entered Class II. One of these was

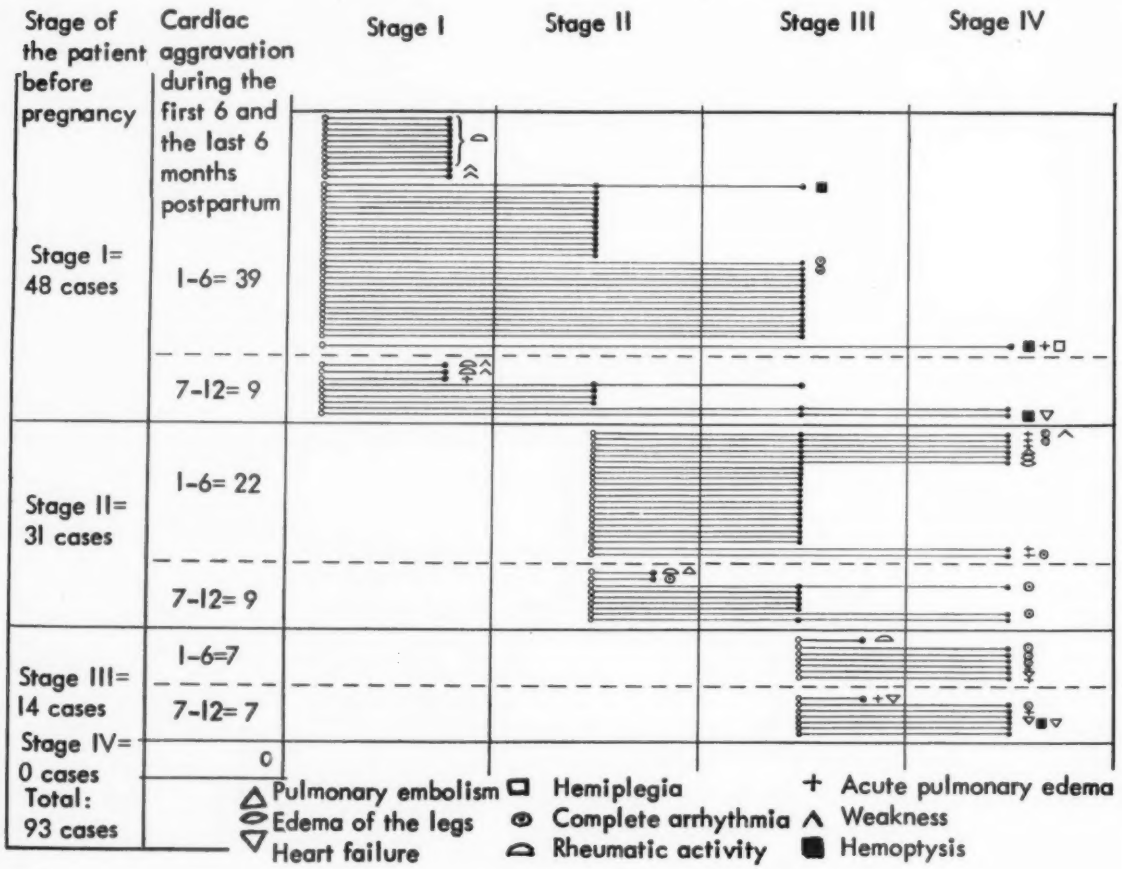

Fig. 1

subsequently reclassified as Class III following an episode of hemoptysis.

Fourteen patients entered Class III, two following the development of auricular fibrillation.

One patient developed frank congestive heart failure (Class IV) with pulmonary edema, hemoptysis and in addition a cerebrovascular accident with resultant hemiplegia.

(b) Cardiac aggravation occurred during the last six months after parturition in nine cases:

Two patients remained in Class I but developed classical acute rheumatic polyarthritis.

One patient who remained in Class I subsequently developed acute pulmonary edema.

Four patients entered Class II. One of these regressed rapidly into Class III.

One patient who evidenced some increased cardiac dysfunction during gestation entered Class III and seven months postpartum she developed frank heart failure (Class IV).

One patient during her second pregnancy deteriorated to Class III and six months after delivery showed a further decline in her cardiac status to Class IV.

(2) *Women with Mitral Disease (Class II) before Pregnancy (31 Cases):* (a) Cardiac aggravation occurred during the first six months after parturition in 22 cases:

Twenty patients entered Class III. Six of them deteriorated rapidly and entered Class IV with the following accidents: acute pulmonary edema (3), auricular fibrillation (2), pedal edema (2), pulmonary embolus (1), serious asthenia (1).

Two patients entered directly into Class IV with severe complications: acute pulmonary edema (1), auricular fibrillation in addition to acute pulmonary edema (1).

(b) Cardiac deterioration was noted during the last six months after parturition in nine cases:

Two patients remained in Class II. However, one of these developed polyarthritis, fever and pulmonary embolism and the other frequent bouts of auricular fibrillation.

Five patients entered Class III and one of these continued rapidly into Class IV with auricular fibrillation.

One patient entered Class IV directly and developed auricular fibrillation.

One patient entered Class III during pregnancy and continued rapidly into Class IV. She improved following a therapeutic abortion at the fifth month but then remained in Class III. Subsequently a mitral commissurotomy was performed.

(3) *Women with Mitral Disease (Class III) During Pregnancy (14 Cases):* (a) Cardiac deterioration occurred during the first six months postpartum in seven cases:

One patient remained in Class III but had many bouts of acute articular rheumatism.

Six women entered Class IV. Three of these developed auricular fibrillation and three others had attacks of acute pulmonary edema, generally associated with the menses.

(b) Cardiac deterioration occurred in the last six months postpartum in seven cases:

One patient remained in Class III but had repeated attacks of pulmonary edema.

Six patients entered Class IV with a variety of complications such as auricular fibrillation, acute pulmonary edema, left and right heart failure (fatal after 5 years), hemoptysis and associated heart failure.

(4) *Women with Mitral Disease (Class IV) During Pregnancy:* Women with mitral disease who have developed frank congestive failure and are in Class IV are advised to prevent pregnancy. No such cases were observed in our series.

Discussion

Significance of the Results: The data is self-explanatory. During 500 pregnancies in women with mitral disease a normal course without postpartum cardiac complications was noted only on 217 occasions. The remaining 283 pregnancies (56.6 per cent) were associated with aggravation of the cardiac disease with or without associated polyarticular rheumatism during the five years following pregnancy. This high incidence of cardiac deterioration appears to us to be quite striking and significant. The evolution in many cases was also accompanied by more severe accidents such as acute pulmonary edema and vascular thrombosis. The majority of instances of deterioration were quite severe, the patients progressing from functional Class I or II into Class III or IV. In no case was there observed a spontaneous improvement in cardiac reserve following pregnancy.

Can a period of five years between a previous pregnancy and the deterioration of the cardiopathy be considered too long a span for ascertaining an absolute cause and effect relationship? We do not believe this. However, to avoid any doubt we have selected arbitrarily only those instances of intensification of the cardiac disease

which occurred during the first year after parturition. When this is done an incidence of 32 per cent aggravation is obtained. It should be noted parenthetically that percentages based either on number of pregnancies or on number of patients are identical over the five year prriod, i.e., 56.6 per cent. They show relatively little discrepancy, 32 and 39 per cent respectively, when related to the first postpartum year.

The Causes of Cardiac Deterioration Following Pregnancy: The lesions of the rheumatic process can either evolve slowly or rapidly, a finding mirrored exactly by the clinical course of the disease. The evolution can be violent and easily noticeable or slow and masked. The inflammatory condition producing the endomyocarditis is responsible for both the valvular and myocardial lesions which in turn burden the heart and cause the hemodynamic difficulties.

The evolution of the rheumatic process is conditioned by various factors. If the concept of infection appears to be losing ground as a causal factor the one of humoral disturbance is now considered more and more as a cause which maintains or creates the inflammatory process. The alterations summarized under the concept of "stress" are equally implicated in the origin of these rheumatic bouts. Pregnancy constitutes both a stress and a humoral disturbance which continues after delivery. In a woman with mitral disease the cardiopathy existing before pregnancy has already modified or weakened her cardiac reserve mechanisms. Therefore, pregnancy, with its specific attendant physiologic changes, becomes a particularly dangerous stress. The unwelcome effect of pregnancy upon the rheumatic patient may occur during or following the pregnancy.

Cardiac Behavior During Pregnancy: Physiologic studies by Hamilton (1949), Werko (1950) and Adams (1954) showed that pregnancy increases the total volume of blood by approximately 25 per cent due to a shift in intracellular fluid. Similarly, there is an increase in cardiac output (up to 30 per cent) accompanied by an elevation of the pulmonary artery pressure. The normal heart can tolerate easily these hemodynamic alterations.[1,4,14] However, the myocardium which is diseased has lost a certain measure of its functional reserve. Although under most circumstances it can maintain an adequate circulation during the gestation period, not infrequently it may manifest symptoms indicative of a further diminution in reserve during the postpartum period. These generally consist of overloading of the lesser circulation leading to pulmonary edema, stagnation of the blood favoring pelvic and lower extremity venous thrombosis, and not infrequently pulmonary emboli,

The authors and their associates[6] have recently completed a study of the occurrence of cardiac complications during pregnancy. It was found that 73 (37.8 per cent) of 193 patients with mitral disease showed no noticeable deterioration of their cardiac status but that the 120 others (61.8 per cent)had circulatory difficulties of varying intensity. One hundred of this latter group developed more severe dyspnea with thoracic pain and palpitation, which reduced their physical capacities but did not endanger their life since medical therapy could maintain or restore a satisfactory cardiovascular balance. In twenty other patients the occurrence of acute pulmonary edema emphasized the seriousness of the cardiac and vascular reactions. In seven of these there were repeated paroxysms during pregnancy, during delivery or postpartum which were so serious that death ensued on one occasion. These seven cases correspond to the classic French "accidents gravido-cardiaques."

Whether minor or important, or whether the above cardiac complications represented the natural evolution of the disease or a direct deleterious effect of pregnancy with increased work of the heart, it is evident that during pregnancy complicated by mitral disease only a small percentage of the pregnancies resulted in serious accidents. In the great majority of cases the cardiac difficulties could be easily controlled by rest and adequate treatment and many of the rheumatic patients carried on their pregnancy without disability.

By considering the effects of pregnancy only in terms of the period of gestation, however, one might jump to the conclusion that the deleterious effect of pregnancy on mitral disease is very limited.[3,9,10,11] Such a conclusion unfortunately is wrong since cardiac deterioration is frequently noted only when the progress of patient is followed during the years following delivery. In

other words, the aggravation of the rheumatic process induced by pregnancy may be seen only after a period of time.

Nature of Deteriorations Resulting From Pregnancy: The deleterious effect of pregnancy on the evolution of the rheumatic heart disease consisted either of bouts of acute polyarticular rheumatism or of a change in the cardiac functional state. In the first category, there were observed episodes of painful polyarticular arthritis with joint swelling and fever, or transient episodes of arthralgia. Bouillaud's disease may appear for the first time following pregnancy or may be superimposed on antecedent valvular disease. These developments have been observed to occur in the same patients during successive pregnancies. Reactivation of rheumatic fever represents the most typical result of the deleterious effect of pregnancy. In our survey there were 29 such cases.

The second category consisted of 64 instances of cardiac deterioration demonstrable by clinical, electrocardiographic and radiologic data. In our analysis of the patient's functional condition we considered the following symptoms important:

(1) *Dyspnea:* This was distinguishable from the typical shortness of breath of pregnancy by its early occurrence, its failure to disappear at rest and its progressive severity as pregnancy proceeded. It also occurred as a manifestation of acute or subacute pulmonary edema.

(2) *Hemoptysis:* This may result from bronchopulmonary arteriovenous anastomoses secondary to bronchial congestion, or from intra-alveolar exudation or from pulmonary infection. The occurrence of hemoptysis in our cases made us suspect the diagnosis of pulmonary embolism. The latter condition always aggravated the underlying heart disease.

(3) *Cardiac Arrhythmia:* Patients may experience regular precordial throbbing during episodes of sinus tachycardia or irregular throbbing during episodes of auricular fibrillation. The latter is a serious complication in pregnancy. Gilchrist and Murray-Lyon,[7] and later Correll and Rosenbaum,[5] have shown that when transient auricular fibrillation occurs during delivery ensuing heart failure may be anticipated.

Summary

(1) The influence of pregnancy on the evolution of mitral valve disease was studied in 233 women who were observed during and after 500 pregnancies for periods up to five years postpartum.

(2) Serious aggravation of the pre-existing cardiopathy occurred in 56.6 per cent of the cases during the postpartum period. A decline in functional capacity occurred in 39.9 per cent of the cases during the first year following parturition and in 16.7 per cent after the first year.

(3) Emphasis is placed on pregnancy as a "stress" to explain the striking deleterious effect upon the evolution of rheumatic heart disease. This was manifested either as acute rheumatic activation or increase in congestive failure with its attendant complications of auricular fibrillation and pulmonary embolism.

(4) The concept of aggravation of mitral valve disease after parturition determines the decisions to be taken in the delicate controversy of "cardiopathy vs. pregnancy."

Conclusion

We may conclude from our study that one out of every three women with mitral disease developed a further reduction in functional capacity within a year following delivery. When the survey is extended to include the subsequent four years, two out of every three women manifested increased cardiac disability. Equally as significant was the finding that regression once having occurred was irreversible. Thus it is our opinion that the therapeutic approach to the problem of "rheumatic heart disease and pregnancy" must be re-evaluated.

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Right Bundle Branch Block and Right Ventricular Hypertrophy*

Electrocardiographic and Vectorcardiographic Diagnosis

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IF ONE reviews the recent articles[1-3] that have appeared in the literature he would admit that there is no agreement on the criteria for the differentiation between right bundle branch block and right ventricular hypertrophy. Vectorcardiographic curves that are characteristic for right ventricular hypertrophy according to Grishman and collaborators have been interpreted by us as those corresponding to right bundle branch block.

It is necessary to distinguish between the clinical significance of a vectorcardiogram and the electrogenesis of the same vectorcardiographic curve; there should be no confusion between clinical vectorcardiography and the electrogenesis of the vector curve. We have the impression that in the studies of Grishman and collaborators there is no attempt at distinction between clinical interpretation and electrogenesis. When we have said that a vectorcardiographic curve corresponds to a right bundle branch block we are referring to the electrogenesis of the curve while at the same time right ventricular hypertrophy may or may not exist.

On the other hand we know that working at a distance (vectorcardiography and clinical electrocardiography) it is impossible to know in detail what is really happening in the heart and that in reality it has been necessary for analysis of tracings taken distally to arrive at a simple physico-mathematic simplification (theorem of Stratton or the Dipole equivalent theory) with experimental background and great clinical application.

Before the experimental work done by Wilson and collaborators in the dog heart, right bundle branch block was diagnosed as left bundle branch block and vice versa. It was necessary to perform experiments with direct leads in the heart of the animal for the correct localization of the bundle branch block. In vectorcardiography, similarly, it is impossible to confirm whether a particular curve corresponds to a bundle branch block or not, if one does not have in mind all the experimental work that has been previously done on bundle branch block, or if one does not take vector curves in an animal after cutting one or the other bundle branch.

In this paper we will consider the three aspects mentioned. We will present, first, right intracavitary ventricular electrocardiograms with corresponding vectorcardiograms. We will also present a vectorcardiographic curve taken in a dog after cutting the right branch of the bundle of His.

MATERIAL AND METHODS

We have studied seven cases. In four the electrocardiogram had two positivities (M shaped complexes) in the right precordial leads (Fig. 4A and 5A) and because of this they were strongly suggestive of right bundle branch block. In two cases, the positivity in V_1 and V_2 showed an initial slurring (Fig. 1A

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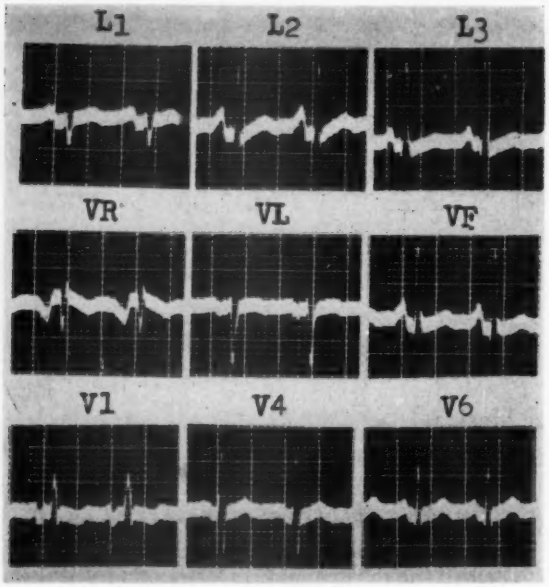

Fig. 1A. Case 1. Age 13. Mitral stenosis. Conventional electrocardiogram.

and 2A) suggestive of right ventricular hypertrophy with the very slight possibility that right bundle branch block also existed.

All of the patients were males aged 7 to 68 years. The clinical and laboratory studies included x-rays, intracardiac catheterization, blood chemistries, urinalysis, vectorcardiograms, and unipolar intracavitary tracings. We employed the Grishman technic for recording vectorcardiograms.

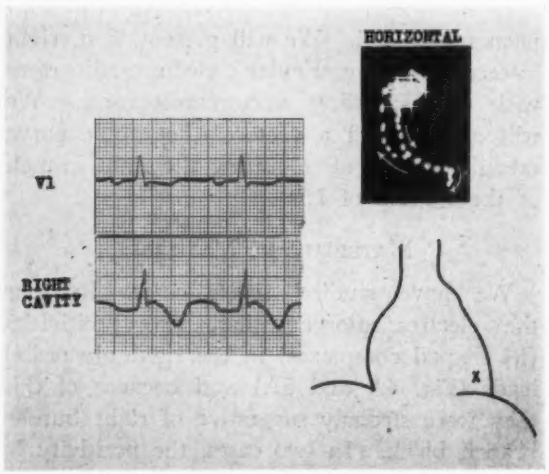

Fig. 1B. Vectorcardiogram and right ventricular cavity lead of same patient.

Catheterization was performed to obtain simultaneous pressure curves, gas studies, and electrocardiographic tracings. We used catheters sized six to eight according to the needs of the case. The sites in which the tracings were registered were minutely checked and confirmed by fluoroscopy and by pressure tracings which always confirmed the continuity of the pressure curve. To illustrate, suppose we were in the right ventricle, on withdrawal of the catheter the pressure curve would show a right atrial pressure tracing. These points were noted on an orthodiagram and later they were transferred to a calculated x-ray image of each patient.

In all the cases intracavitary electrocardiographic tracings were taken in three different locations as follows: (1) at the level of the pulmonary conus; (2) in the middle of the right ventricle; (3) at the apex of the right ventricle.

Simultaneously V_1 was taken as a reference lead. Several of the tracings were discarded because they were accompanied by an accentuated imbalance of the RS-T segment produced by the pressure of the exploring electrode against the subendocardial muscle. This is the reason why in some of the figures not all the tracings recorded in the right ventricle are shown.

In a dog the right branch of the His bundle was severed and we registered the vector curve in the three planes using the Grishman technic. On the thorax of an animal it is difficult to construct a cube but notwithstanding this limitation we tried to place the electrodes so that they were equidistant from the cardiac mass.

Results

The graphs which are shown in Fig. 1A and 1B are those taken from a 13-year-old patient with mitral stenosis. In lead V_1 the ventricular complex is of the Rs type with a negative T wave, very suggestive of right ventricular hypertrophy (Fig. 1A). The vectorcardiogram obtained in the horizontal plane is definitely abnormal because of its anterior projection and because of the clockwise rotation during all the development of the QRS loop (Fig. 1B).

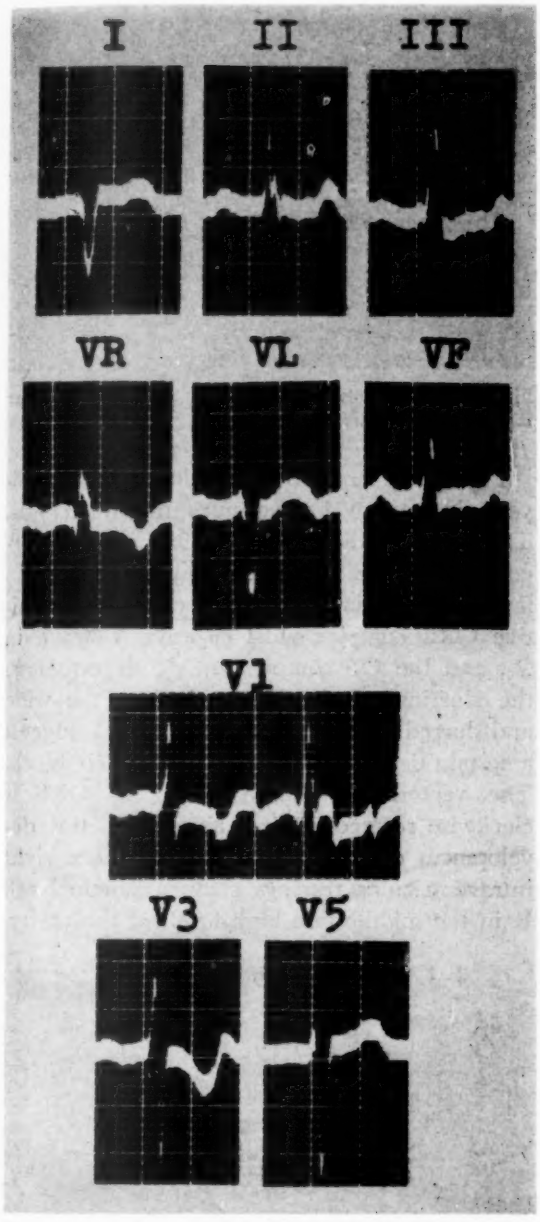

Fig. 2A. Case 2. Age 12. Mitral stenosis and double tricuspid lesion. Conventional electrocardiogram.

The tracing obtained near the apex of the right ventricular cavity is essentially positive (type Rs) and having an intrinsic deflection of .035 to .040 second.

Fig. 2A and 2B were taken in a 12-year-old patient with a rheumatic mitral valve lesion. The electrocardiogram is very typical of right ventricular hypertrophy (Fig. 2A). In V_1 there is an Rs complex; at times it seems to

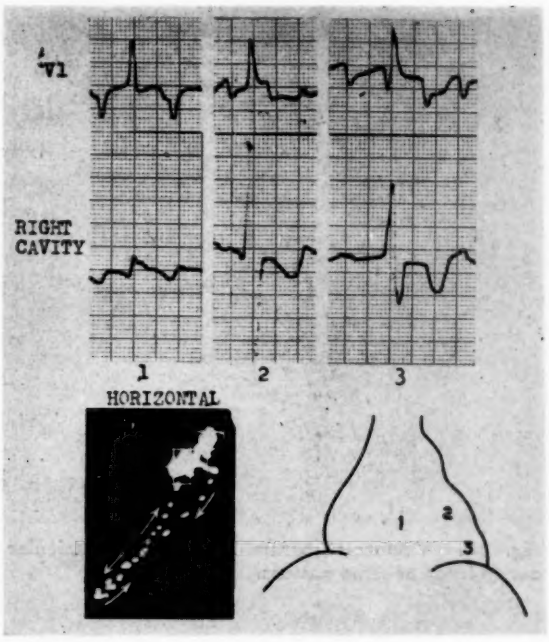

Fig. 2B. Vectorcardiogram and right ventricular cavity leads of same patient.

be QR, but in reality the apparent initial negativity is derived from auricular flutter waves. The marked deviation of the electrical axis to the right, the negative values of the index of Lewis, the small R with deep S in V_5, all are

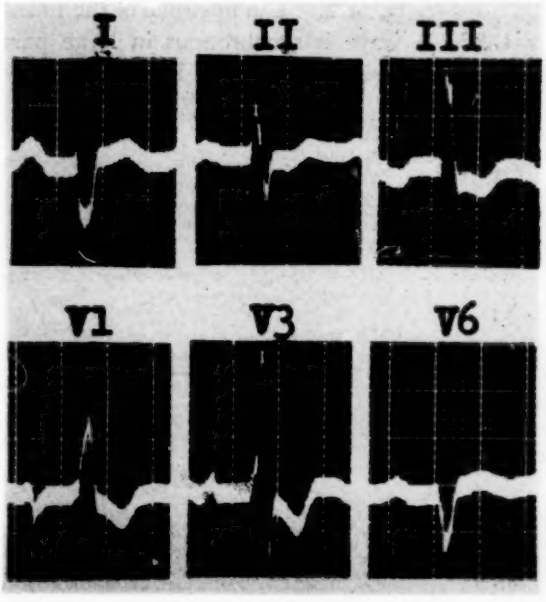

Fig. 3A. Case 3. Age 18. Pure mitral stenosis. Conventional electrocardiogram.

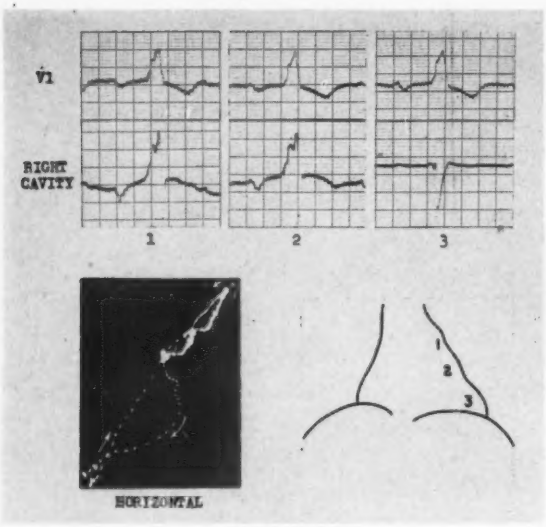

Fig. 3B. Vectorcardiogram and right ventricular cavity leads of same patient.

confirmatory data for the diagnosis of right ventricular hypertrophy. The horizontal vectorcardiogram (Fig. 2B) is displaced anteriorly and to the right and shows clockwise rotation during the greater part of its development. The tracings taken in the right ventricular cavity (points 2 and 3 of the schema of Fig. 2B) show complexes of the RS type or qRs with an intrinsic deflection of 0.04 sec for point 3, and 0.05 sec for point 2. The upstroke of the intracavitary R wave is synchronous in large part with the ascending limb of the R in V_1.

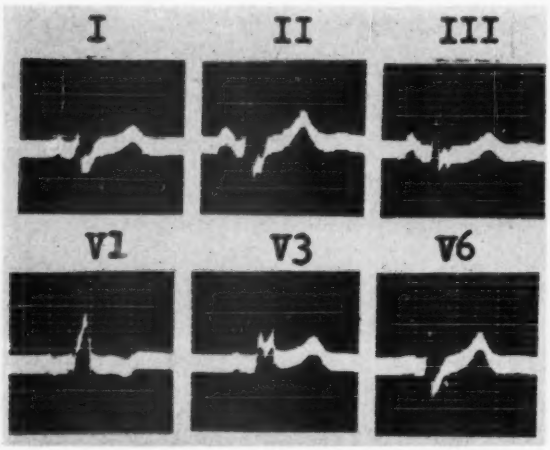

Fig. 4A. Case 4. Age 68. Chronic cor pulmonale. Conventional electrocardiogram.

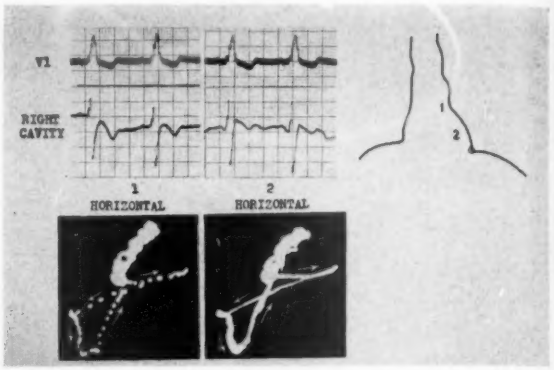

Fig. 4B. Vectorcardiogram and right ventricular leads of same patient.

Figures 3A and 3B were taken from an 18-year-old patient having pure mitral stenosis. The electrocardiogram (Fig. 3A) is very suggestive of right ventricular hypertrophy. In favor of this diagnosis is the completely positive QRS complex with negative T wave in V_1, and the QS complex in V_6, nevertheless, the slurring of the R in V_3 and the wide and slurred S wave in V_6 and Lead I suggest a certain degree of right bundle branch block. The vectorcardiographic sweep of QRS is clockwise rotated during almost all the development of the curve (Fig. 3B). The right intraventricular tracings show a notched tall R in the middle and high levels of the cavity.

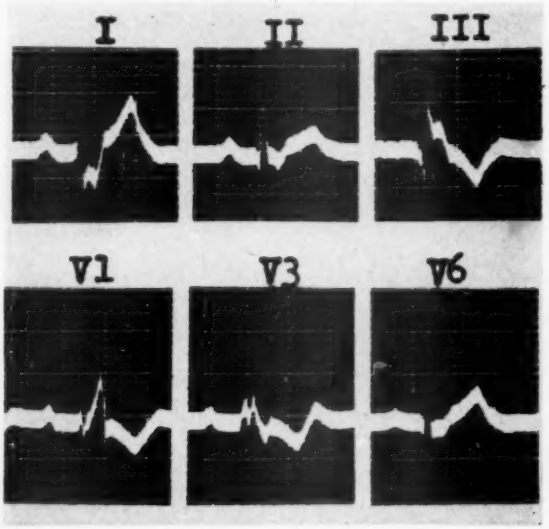

Fig. 5A. Case 5. Age 9. Rheumatic myocarditis and mitral insufficiency. Conventional electrocardiogram.

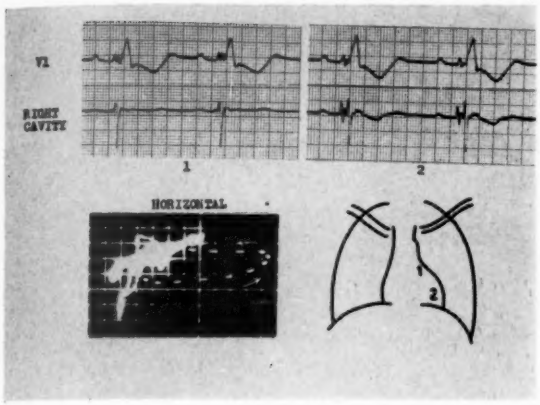

Fig. 5B. Vectorcardiogram and right ventricular cavity leads of same patient.

The intrinsic deflection is 0.08 sec after the onset of QRS. In the low intracavitary leads there are too small positivities with an intrinsic deflection of 0.04 sec.

Fig. 4A and 4B are those of a 68-year-old patient with arteriosclerotic heart disease, pulmonary emphysema and chronic cor pulmonale. The ventricular complex in V_1 is positive of the rsR type with a negative T wave strongly suggestive of right bundle branch block (Fig. 4A). The remainder of the cardiogram affirms this diagnosis. The horizontal vectorcardiogram is displaced anteriorly with clockwise rotation of the loop in the first portion and with slurring and slow development in the final portions (Fig. 8).

The tracings obtained in the right ventricular cavity are type RS in the upper portions of the cavity and qRs in the lower level. The intrinsic deflection is inscribed 0.045 sec after the onset of QRS in the tracings obtained in the apex of the cavity.

Fig. 5A and 5B are those of a nine-year-old boy with a clinical diagnosis of active rheumatic myocarditis and mitral insufficiency. The possibility of an interatrial septal defect which could not be demonstrated by catheterization also existed. The electrocardiogram (Fig. 5A) and in particular lead V_1 are very characteristic of a marked right bundle branch block. The vectorcardiographic curve (Fig. 5B) obtained in the horizontal plane is rotated counterclockwise without demonstrable slurring in its development. The intraventricular tracings (Fig. 5B) are of the rsRs type with a delay of up to 0.06 sec for the intrinsic deflection.

Figures 6A and 6B are those of a 42-year-old patient having atrial fibrillation and a double mitrial lesion. The electrocardiogram suggests an incomplete right bundle branch block (Fig. 6A) because of the presence of two positivities with a significant delay of the intrinsicoid deflection. The vectorcardiogram rotates in the counterclockwise direction.

The intraventricular tracings show two positive deflections in the middle and high portions of the right ventricular cavity. In point 5 (low level of the right ventricular cavity) the tracing shows a marked slurring on the R wave with an intrinsic deflection of 0.04 second.

The studies shown in Fig. 7A and 7B are those of a seven-year-old boy with a "probable normal heart." The electrocardiogram shows in V_1 an M-shaped complex suspicious or sug-

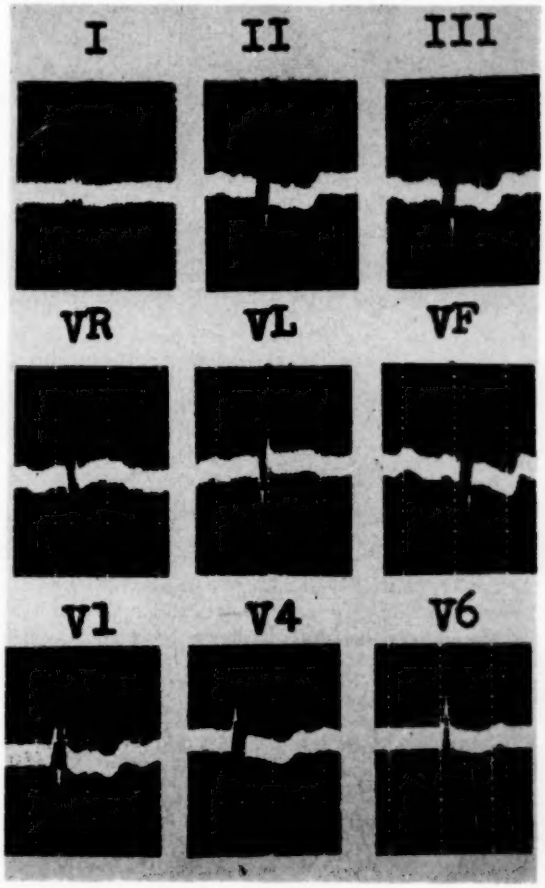

Fig. 6A. Case 6. Age 42. Mitral stenosis and insufficiency. Conventional electrocardiogram.

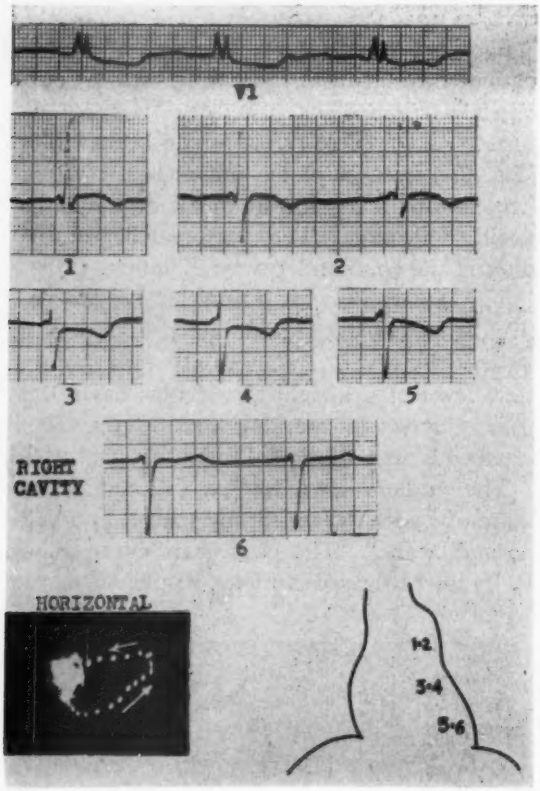

Fig. 6B. Vectorcardiogram and right ventricular cavity leads of same patient.

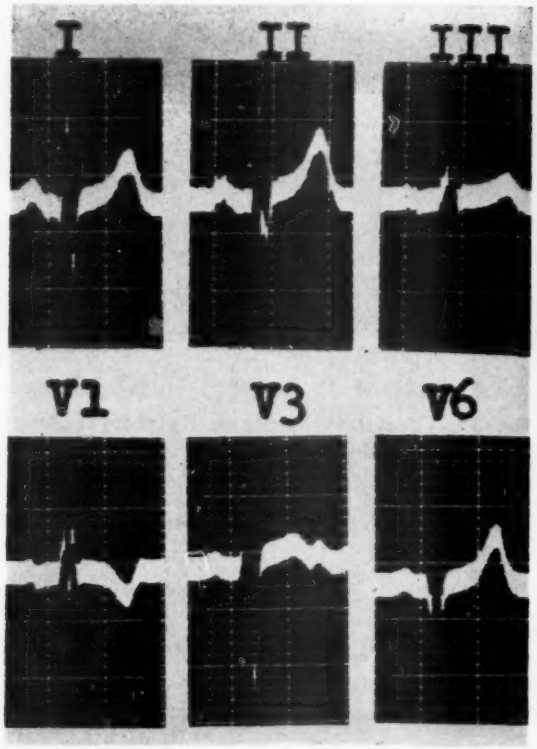

Fig. 7A. Case 7. Age 7. No cardiac disease. Conventional electrocardiogram.

gestive of incomplete right bundle branch block (Fig. 7A). The vectorcardiographic loop of QRS goes in a counterclockwise direction in its terminal portions. The right intraventricular unipolar leads at the various levels show complexes of the rS type without delay of the intrinsic deflection.

Summary of the Clinical Histories of the Cases Studied

Case 1. M. L. G. Age 13. Diagnosis: Pure mitral stenosis; pulmonary artery hypertension 3 plus and venocapillary hypertension 2 plus.

Two years previous the patient had two sudden episodes of loss of consciousness without any apparent cause and leaving no sequelae. For the last year he had been having dyspnea on great effort. There were no other complaints.

X-ray: Cardiomegaly 2 plus with right ventricular hypertrophy 2 plus, right atrium and left atrium 1 plus. Hilar accentuation 2 plus without hilar dance. Pulmonary conus 2 plus.

Electrocardiogram: See Figure 1A.

Cardiac Catheterization: Right ventricle: systolic pressure 87 mm Hg, diastolic 6 and mean 50. Pulmonary artery: systolic pressure 86 mm Hg, diastolic 51 and mean 63. Left brachial artery: systolic pressure 95 mm Hg and diastolic 50.

Commissurotomy proved the existence of a pure mitral stenosis.

Case 2. J. D. T. Age 12. Diagnosis: Mitral stenosis with double tricuspid lesion. Pulmonary artery hypertension 3 plus and venocapillary pressure 2 plus.

At the age of eight, the patient had his first attack of rheumatic fever. Two years later dyspnea on great effort, palpitations and maleolar edema at night appeared. At that time the patient's mother noted a thoracic deformity with bulging of the precordium. One year later (1953), dyspnea appeared on slight to moderate effort. Frequent cough with bloody sputum was also noted. At this time it was observed in the outpatient department that the patient had atrial fibrillation.

During hospitalization, the patient had multiple pulmonary infarcts.

X-ray: Cardiomegaly 3 plus. Right ventricular hypertrophy 3 plus, right atrial hypertrophy 2 plus. accentuated hilar markings 2 plus, prominence of pulmonary conus 2–3 plus.

Electrocardiogram: See Figure 2A.

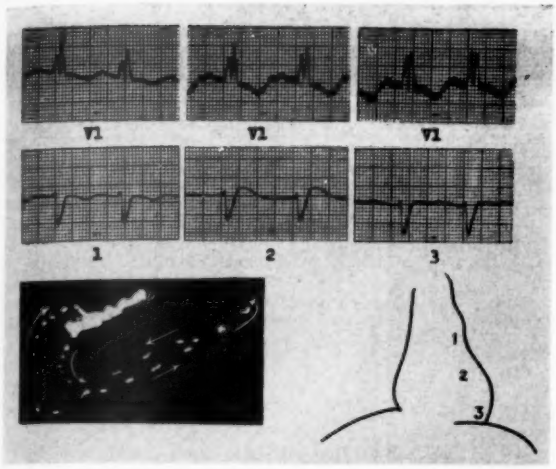

Fig. 7B. Vectorcardiogram and right ventricular cavity leads of same patient.

Cardiac Catheterization: Right ventricular systolic pressure 83 mm Hg, diastolic 11 and mean 41. Pulmonary artery pressure: systolic 78 mm Hg, diastolic 48 and mean 58.

CASE 3. I. V. P. 18-years old. Diagnosis: Pure mitral stenosis. Pulmonary hypertension 3 plus and venocapillary hypertension 1 plus.

For the past five years, the patient had dyspnea on great effort (climbing stairs, walking four to five blocks). His condition remained unchanged until a year ago when dyspnea appeared on moderate exertion. At the same time there appeared palpitations which were sudden in onset and gradual in termination, lasting a short time. There was no edema.

X-ray: Cardiomegaly 2 plus. Right ventricular hypertrophy. Pulmonary conus 2 plus. Left atrium 2 plus and right atrium 2 plus.

Electrocardiogram: See Figure 3A.

Cardiac Catheterization: Right ventricle: systolic pressure 126 mm Hg, diastolic 7 and mean 57. Pulmonary artery: Systolic pressure 126 mm Hg, diastolic 55.2 and mean 81. Left brachial artery: Systolic pressure 99 mm Hg, diastolic 73.7 and mean 70.

CASE 4. H. E. R. 68-years old. Diagnosis: Generalized arteriosclerosis, arteriosclerotic heart disease and chronic cor pulmonale.

The patient's complaints started six years previous. At that time, he noted palpitations of sudden onset and gradual termination which were accompanied by a sensation of precordial oppression, anxiety and cold sweat. The patient improved with medical treatment and remained asymptomatic for three years. Two years previous, while at his office, the patient experienced a recurrence of previous symptoms, accompanied by loss of consciousness for half an hour. Since 1954, there were frequent recurrences of similar episodes accompanied by anxiety, cold sweat and precordial distress radiating to the left arm. Since that time there was also dyspnea on mild effort.

The patient had had recurrent bronchitis for the preceding 30 years.

Electrocardiogram: See Figure 4A.

X-ray: Cardiomegaly 1 plus with right ventricular hypertrophy. Pulmonary conus 2 plus enlarged. Hilar markings 2 plus accentuated with forceful pulsations.

Cardiac Catheterization: Right ventricle: systolic pressure 20 mm Hg, diastolic pressure 1 and mean 4. Pulmonary artery: systolic pressure 20 mm Hg, diastolic 6 and mean 10.

CASE 5. J. S. D. 9-years old. Diagnosis: Active rheumatic myocarditis, mitral insufficiency and probable interatrial septal defect. In 1954 the patient had the first episode of rheumatic fever lasting six months. He was treated with cortisone and improved. However, there was still dyspnea on great effort. In June 1956 migratory polyarthritis, fever, sweating and exaggeration of dyspnea were his symptoms. On physical examination, there was a systolic murmur at the base with a wide and constant reduplication of the pulmonary second sound. These findings were suggestive of an interatrial septal defect but this diagnosis was not confirmed at cardiac catheterization. The presence of active rheumatic fever in the presence of a grade 3 systolic murmur (apical) radiating to the axilla suggested the possibility of rheumatic myocarditis rather than an organic mitral insufficiency.

X-ray: No cardiomegaly. Right atrium showed forceful pulsations. Accentuated hilar markings 1–2 plus with 2 plus pulsations.

Electrocardiogram: See Figure 5A.

Cardiac Catheterization: Right ventricle systolic pressure 33 mm Hg, diastolic 0.4, mean 10. Pulmonary artery: systolic pressure 31 mm Hg, diastolic 8, mean 18. Pulmonary capillary: 2.24 mm Hg. Right atrium: 2.8 mm Hg.

Catheterization revealed no abnormalities in gas content of blood taken from the cardiac chambers.

CASE 6. A. C. P. 42-years old. Diagnosis: Double mitral lesion with predominant mitral stenosis. Pulmonary artery hypertension 3 plus and venocapillary hypertension 1 plus.

In the preceding eight years, dyspnea had shown progression appearing now on slight effort. Lately, palpitations have appeared. Maleolar edema is relieved by digitalis, but this therapy has not changed the patient's functional capacity.

X-ray: Cardiomegaly 2 plus. Right ventricular hypertrophy 2 plus. Left atrial hypertrophy 2 plus. Left ventricular hypertrophy 1 plus. Pulmonary conus 1 plus. Hilar markings 4 plus.

Electrocardiogram: See Figure 6A.

Cardiac Catheterization: Right ventricle: systolic pressure 60.2 mm Hg, diastolic minus 2 and mean 20. Pulmonary artery: systolic pressure 60.2, diastolic 27.6, mean 44.

The patient was submitted to commissurotomy, at

which time a double mitral lesion was observed with a significant degree of mitral insufficiency and valvular calcification.

CASE 7. F. G. Q. 7-years old. Diagnosis: Probably normal heart.

Normal full term infant with normal delivery and normal subsequent development. The mother brought the child for observation because she noted that the child tired easily when he ran or cried. The child had not had dyspnea, edema or palpitations.

X-ray: There was no cardiac or chamber enlargement. There were normal hilar markings. There was slight prominence of the pulmonary conus not incompatible with normalcy for a child this age.

Electrocardiogram: See Figure 7A.

Cardiac Catheterization: Right ventricle systolic pressure 28 mm Hg, diastolic 1 and mean 1.6. Pulmonary artery: systolic pressure 24 mm Hg, diastolic 12, mean 14.

There was no abnormality in gas analysis.

ELECTROCARDIOGRAM OF THE DOG AFTER CUTTING THE RIGHT BRANCH OF THE BUNDLE OF HIS

Figure 8 shows the vectorcardiogram of a dog after cutting the right branch of the bundle of His. The horizontal plane of the vectorcardiogram is displaced to the right and anteriorly, showing clockwise rotation in the major part of its development; although at the terminus of the graph there is a slurred portion showing counterclockwise rotation. This curve is similar to those of the clinical cases which are shown in Figures 3B and 4B.

DISCUSSION

In order to correctly interpret a vectorcardiogram we consider a knowledge of the sequence of the activation process indispensable. A simultaneous electrocardiographic curve will help us greatly since the interpretation of the electrocardiogram has as a base a great deal of accumulated investigative material dating from the beginnings of electrocardiography.[5] It is not reasonable to discard so much knowledge without good cause unless new experimentation, more careful and more complete, can be substituted for it.

To say that a vectorcardiogram does not show right bundle branch block notwithstanding that the electrocardiogram shows characteristic morphology of said block in V_1 and V_2, is to forget or to disregard the investigation of so many years.

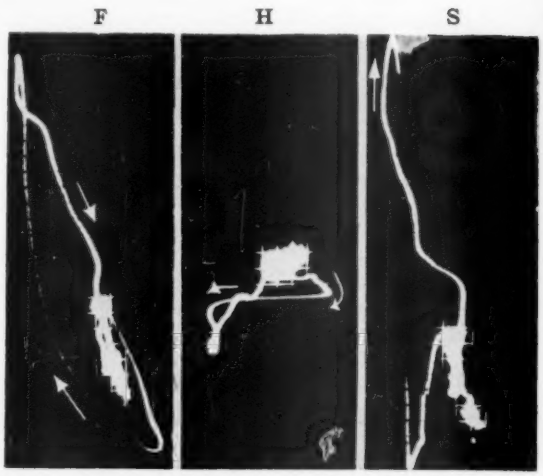

Fig. 8. Electrocardiogram of a dog after cutting the right branch of the bundle of His. From left to right, frontal, horizontal and saggital planes.

It is even worse to uphold such a view without new experiments. We should be careful before we accept such dangerous views which involve so many branches of medicine.

For the study of the sequence of the activation process, there is for the moment no better work than that done with close bipolar leads on the surface and in the mass of the heart.[4] This type of investigation can only be carried out in animals, at least for the time being.

In the human heart, one is able to study the intracavitary potential with unipolar leads. These leads are very useful and serve to clarify in the great majority of cases whether or not bundle branch block is present. It should not be said, as have some investigators, that unipolar leads are not useful and are conducive to error. These leads have some limitations, but are very useful and are related to close bipolar leads by physical laws which have been established by investigation.[4]

Let us now observe the right intraventricular unipolar morphology in right bundle branch block and right ventricular hypertrophy.

RIGHT INTRAVENTRICULAR UNIPOLAR MORPHOLOGY IN RIGHT VENTRICULAR HYPERTROPHY

(1) If the hypertrophy is of the free wall, the vectors of this wall will be larger and since they proceed from cavity to epicardium will produce a deep intracavitary S wave (Fig. 9).

(2) If the hypertrophy is of the right septal

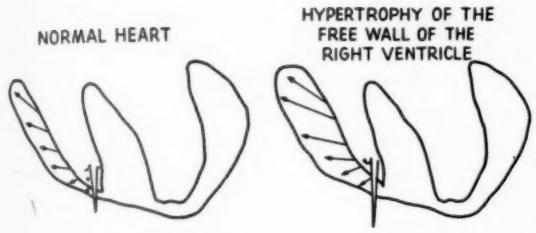

Fig. 9. Effect of hypertrophy of the free wall of the right ventricle on right ventricular vectors and cavity lead.

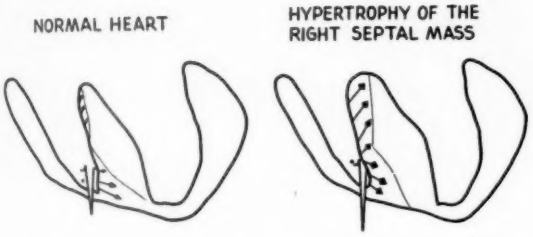

Fig. 10. Effect of hypertrophy of the right septal mass on right ventricular vectors and cavity lead.

mass, the corresponding vectors of activation will be greater and since they proceed in a direction away from the cavity will give a deeper intracavitary S wave (Fig. 10).

As we have just seen, hypertrophy of either the free wall or the septum will produce an increase in the negativity of the intracavitary tracings.

UNIPOLAR MORPHOLOGY FROM THE RIGHT VENTRICULAR CAVITY IN RIGHT BUNDLE BRANCH BLOCK

We have demonstrated in our department[4,6] that in cases of high degree of block there is a jump of the wave from the normally activated septal mass to the septal mass which is blocked. While the jump is occurring, the septal mass which is not blocked is depolarized (negative), and the blocked septal mass is still polarized (positive), forming thus a large vector which goes from the negative mass (not blocked) to the positive (blocked). For this reason in cases of right bundle branch block the vector will point to the lower level of the right intraventricular cavity. Therefore, in right bundle branch block, an increase in the voltage of R and a delay in the intrinsicoid deflection must be expected and is even greater with higher degrees of block. Since the septal mass is activated from the bottom up, in the presence of right bundle branch block one finds greater positivities in the higher portions of the right ventricular cavity. If the major positivity is interrupted by the forces of activation of the left ventricle, two positivities can be recorded. These concepts are in keeping with the right intraventricular tracings which we have described in right bundle branch block and which are of the type RS, Rs, qRS or rsRS.

DIFFICULTIES IN THE INTERPRETATION OF THE TRACINGS TAKEN FROM THE RIGHT VENTRICULAR CAVITY IN CASES OF RIGHT BUNDLE BRANCH BLOCK

The difficulties of interpretation stem from the complex electrical bipartition of the interventricular septum. Recent experimental work done in our department[6] demonstrates that in exploring the posterior-superior portions of the interventricular septum proximal to the tricuspid valve one is exploring the left septal mass in which negative complexes predominate when there is right bundle branch block.

It is necessary to advance the tip of the catheter to the lowest portions of the right ventricular cavity close to the interventricular septum; these sites are not explored usually when the catheter is advanced to the outflow tract of the right ventricle and pulmonary artery. Unless this fact is kept in mind, an error may be made. In the case shown in Figures 7A and 7B with M-shaped complexes in V_1 and with essentially normal tracings in the right cavity, the possibility is suggested that we had explored fundamentally the left septal mass (see p. 66). Perhaps future investigations with the heart open will allow us to overcome these disadvantages in exploration.

In accord with the criteria which we have selected for the diagnosis of right bundle branch block, we can confirm that at least six of the seven cases presented showed conduction defects. In these we have found three different forms of vectorcardiographic rotation in the horizontal plane: clockwise, counterclockwise and mixed rotation. We believe that this is

sufficient to state that there is no loop rotation which might be considered as exclusively representative of right bundle branch block.

In two of the cases, the electrocardiogram was characteristic of right ventricular hypertrophy without suggestion of right bundle branch block (Figures 1A, 1B, 2A, 2B). The intracavitary tracing nevertheless showed a tall R with a marked delay of the intrinsicoid deflection which obliges one to consider the presence of an important degree of right bundle branch block. These findings reinforce the points of view put forth some time ago that the electrical picture of pure hypertrophy is unusual and that one always has to consider a degree of right bundle branch block.

In the case of Figures 7A and 7B, the electrocardiogram suggests incomplete right bundle branch block, nevertheless the intracavitary tracing shows essentially negative ventricular complexes at all levels. Two different explanations can be offered:

(1) Intracavitary leads did not explore the right septal mass (see above).

(2) We were not dealing with right bundle branch block and the M-shaped complex in V_1 can be explained by the three main vectors that constitute normal ventricular activation (as described by Peñaloza and Tranchesi).[7] In order to admit this explanation it is necessary that the exploring electrode in V_1 records fundamentally the potential variations of the upper portions of the right ventricular epicardium.

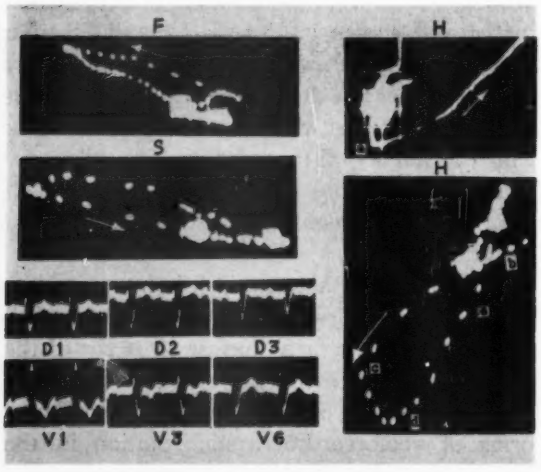

Fig. 11. Conventional electrocardiogram and vectorcardiogram in right bundle branch block.

The vectorcardiographic study done in a dog after severing the right branch of the bundle of His is very characteristic in the horizontal plane. The curve in this plane (Fig. 8) is very similar to those shown in the clinical cases seen in Figures 3B and 4B. These tracings especially show the morphology described by others as typical of right ventricular hypertrophy. This interpretation seems to be correct from the clinical point of view, but does not take into account the electrogenesis of the curve.

CORRELATION BETWEEN THE HORIZONTAL VECTORCARDIOGRAM OF A CLINICAL CASE AND THE SEQUENCE OF THE VENTRICULAR ACTIVATION PROCESS

Figure 11 shows a typical case of right bundle branch block. In the curve four main portions can be distinguished: the first ("a" of Figure 11; the first portion of the horizontal vectorcardiogram is magnified) corresponds to the activation of the left septal mass, and like the activation process of this region is directed toward the right and forward.[4] The second (between "a" and "b" of Fig. 11, with the horizontal vectorcardiogram magnified in its initial portion) is directed to the left and backward as is the activation process of the left ventricle.[4] The third (between "b" and "c" of Figure 11) is directed forward and to the right, corresponding principally to the "jump" wave going from the left to the right ventricle but also in part to the activation of the free right ventricular wall.[4] The last fourth portion ("d" and "e" of Figure 11) in the horizontal plane corresponds fundamentally to some additional contribution of the concluding septal activation.

Summary

The right intracavity leads show a great incidence of incomplete or complete right bundle branch block in cases with electrocardiograms very suggestive of right ventricular hypertrophy. In these instances we have found three different forms of rotation of the vectorcardiographic loop in the horizontal plane: clockwise, counterclockwise and mixed rotation. We believe that this is sufficient to state that there is no loop ro-

tation which might be considered as exclusively representative of right bundle branch block.

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Left Atrial Electrokymograms and Pressure Pulses in Mitral Valve Disease*

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Left Atrial Electrokymogram (la eky)

The electrokymogram of the left atrium was described by Luisada *et al.*[1] in normal subjects. Its pattern consists of a negative wave in presystole (atrial contraction) and a negative wave in systole (ventricular traction on the mitral valve). A small positive notch (A-V wave) is visible between them and reveals the closure of the mitral valve. The end of the systolic wave follows the 2nd aortic sound by 0.06–0.08 sec and coincides with the opening of the mitral valve (V-wave) (Fig. 1).

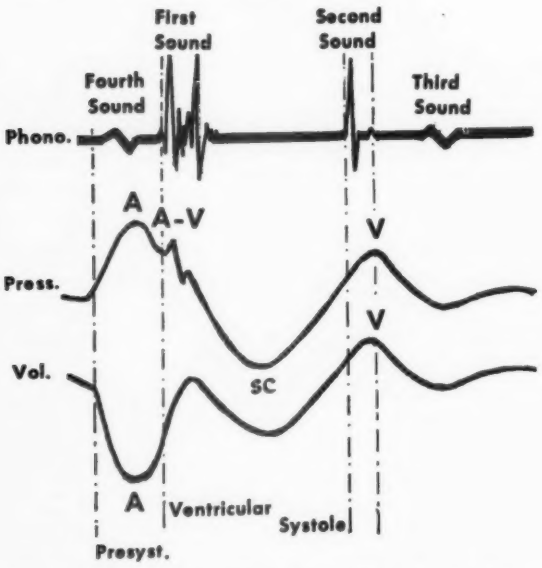

Fig. 1. Schematic pattern of normal left atrial pressure as compared with the normal tracing of volume. The latter is practically identical with an electrokymogram of the left atrium.

A typical abnormal pattern was subsequently described by Luisada and Fleischner[2] in mitral valve patients. This pattern consisted of a plateau-like, rectangular wave during ventricular systole (Fig. 2 and 3). As the pattern resembled that of intraventricular pressure, it was interpreted as due to regurgitation of blood across the mitral valve, even though some of the cases had obvious mitral stenosis. This

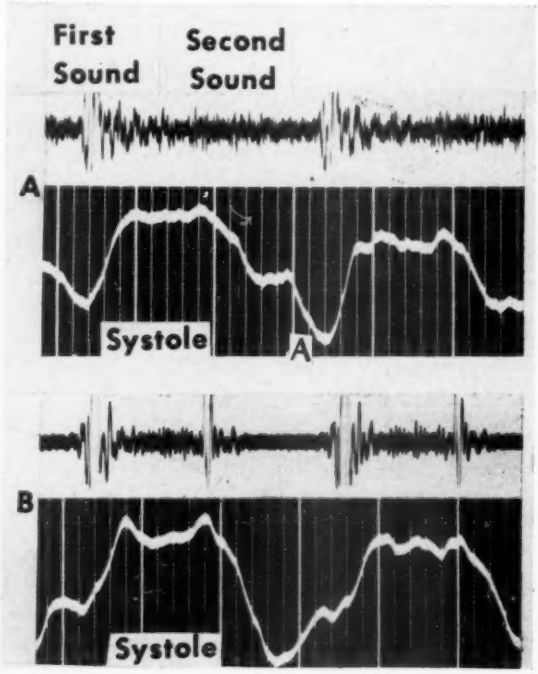

Fig. 2. The plateau pattern of mitral regurgitation in the left atrial electrokymogram. (From Luisada, A. A., and Fleischner, F. G.: *Am. J. Med.* 9: 791, 1948).

* From the Division of Cardiology, The Chicago Medical School, Mount Sinai Hospital, Chicago, Illinois.

This study was conducted during the tenure of a Teaching Grant of the National Heart Institute, U.S.P.H.S., and with the help of grants of the Chicago Heart Association and the Lasdon Foundation of New York.

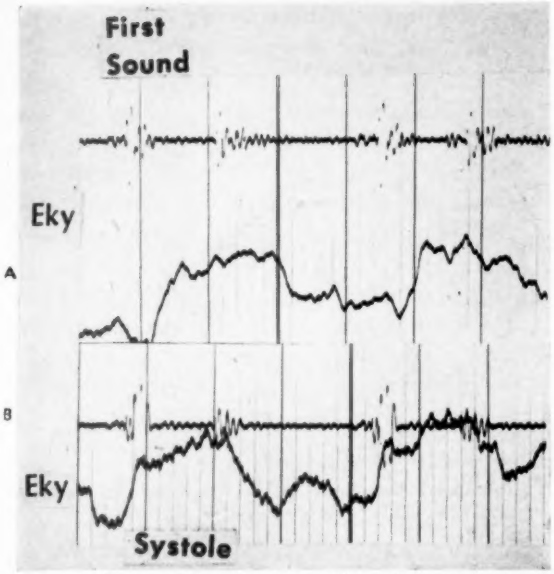

Fig. 3. Late plateau before (A) and early plateau after (B) mitral commissurotomy in a case of mitral stenosis with moderate insufficiency. Electrokymograms of left atrium.

interpretation was subsequently confirmed by several workers.[3–9] On the other hand, others[10–14] did not accept such interpretation for various reasons: (1) Such a pattern was found occasionally in normal subjects and in some cases where the surgeon felt no regurgitant jet; (2) a more typical plateau was described in cases with "pure" stenosis than in cases with obvious insufficiency; (3) a plateau was found in cases of atrial fibrillation supposedly without mitral lesions; (4) the pattern of left atrial pressure in experimental mitral lesions[15] was different from the plateau pattern.

Following a description of the technical pitfalls of electrokymography,[16] our group revised the problem.[17] Multiple left atrial tracings in several projections and at various levels, recording of both border tracings and densograms, at high speed and with simultaneous phonocardiograms, prevented possible technical errors. A study of 21 clinical cases with mitral valve disease before and after surgery[17] led to description of two, somewhat different, patterns (Fig. 3): (1) A late-plateau pattern in mitral stenosis plus insufficiency; (2) an early plateau pattern in free mitral regurgitation. The former pattern usually changed to the latter after mitral surgery.[17]

It was recognized that no typical pattern existed for "pure" mitral stenosis and that, in spite of calibration, it was difficult to quantitate the severity of regurgitation. It should be kept in mind that the tremendous power of magnification of the electrokymograph tends to overemphasize regurgitation while multiple causes inherent in cardiac surgery tend to underestimate regurgitation on the operative table

Normal Left Atrial Pressure Pulse

Left atrial pressure pulses have been recorded in cases of atrial septal defect.[18,19] Direct puncture during thoracotomy allowed Wynn *et al.*[20] a study in normal subjects. Later on, tracings were recorded by transbronchial puncture[21–23] while Bjoerk[24,25] and Kent *et al.*[26] used the posterior transthoracic approach. Other important contributions have been published.[27–32]

We have recorded this tracing in two patients who proved to have no significant lesion of the mitral valve. The pattern, similar to the scheme of Fig. 1A, is as follows (Fig. 6A): There is a large positive A-wave in presystole; a diphasic or triphasic notch during the first part of the 1st heart sound (closure of mitral valve—wave A-V);* then a rounded, slow, negative wave (systolic collapse) culminating in the positive V-wave. The peak of the latter takes place about 0.08 sec after the main vibration of the 2nd heart sound and is lower than the A-wave.

Electrokymogram and Pressure Tracings in Experimental Mitral Defects

Before undertaking the present study, it was considered useful to compare the two above types of tracings in experimental mitral valve defects. Left atrial electrokymograms, left atrial pressure tracings and pulmonary artery wedge pressure tracings were studied by Haring, Liu, and Trace[34] in this laboratory. The study was undertaken in 32 operated dogs, eight of which survived for two weeks or more and were repeatedly studied. It was observed that, while mitral stenosis, pure or with insufficiency, severely raised left atrial mean and pulmonary

* This notch has been called C-wave by others. We do not believe that such a connotation is justified in the case of the left atrium (see *Luisada and Liu*).[33]

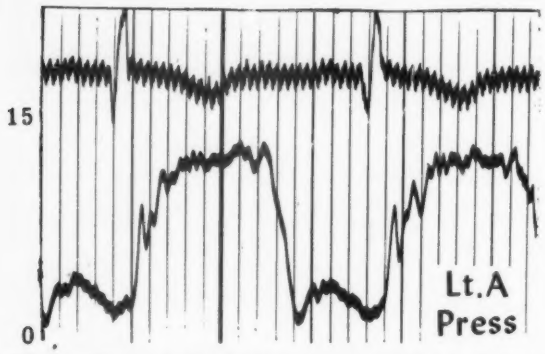

Fig. 4. Dog. Left atrial pressure tracing and electrocardiogram 1 week after establishment of mitral insufficiency (early plateau). (By permission, from Haring *et al.*: *Circulation Res.* 4: 381, 1956).

artery wedge pressures, pure mitral insufficiency did so to a much lesser extent. It was determined that *pure mitral stenosis*, while raising the left atrial pressure during ventricular diastole, left the left atrial pattern relatively unchanged. Taller A- and V-waves and a steeper rise during the second part of the systolic collapse were the only modifications. *Pure mitral insufficiency* was revealed by the substitution of a squarish plateau for the systolic collapse of the left atrial pattern (Fig. 4). In general, the rise of the plateau was rapid (early plateau) but a more gradual rise occurred in two animals. In *mitral insufficiency and stenosis*, the same abnormal patterns were found, with the exception that the rise and fall of the plateau wave were more gradual (late-plateau) and that diastolic pressure was higher than in normal animals. These findings were confirmed by Crawshaw *et al.*[35]

The electrokymograms of the left atrium were similar to the pressure pulses of this chamber. They revealed a plateau-like wave instead of the normal collapse during ventricular systole whenever there was regurgitation. If no mitral stenosis was associated, the plateau was of an "early" type. If there also was stenosis, the plateau was of a "late" type. Pure mitral stenosis had *no* plateau. In one instance, the pressure tracing rose more slowly than the electrokymogram (Fig. 5).

General Considerations

Dynamics of the left atrium is revealed by LA electrokymograms and LA pressures as in Table I. Atrial contraction is revealed in the opposite way by the tracings of pressure and volume (electrokymograms) i.e., increase of pressure-decrease of volume (Fig. 1). During most of diastole and all of systole, the two tracings reveal with similar waves the passive movements of the atrial wall, changes of volume usually accompanying changes of pressure. However, one possibility should be kept in mind. The left atrium has an elastic wall. A sudden jet under pressure (mitral regurgitation) may distend the wall in a remarkable way with little increase in pressure. This was actually noted in one of the animal experiments (Fig. 5) where a rapid increase in volume was accompanied by a slow increase in pressure. Theoretically, this phenomenon might occur in pure mitral insufficiency (where diastolic pressure is normal), not in mitral stenosis with insufficiency (where a high diastolic pressure would keep the wall under tension and prevent further excessive distention).

Material and Method

Our study was conducted in 17 cases. Left heart catheterization was performed in the prone position according to Fisher's modification of Bjoerk's technic. A No. 18, thin-walled, 6 inch long needle was introduced in the left atrium from the right paravertebral space (seventh to ninth i.c.s.).

The *pressure* was recorded at 25 mm/sec by means of a P 23 D Statham strain gauge and a cathode-ray oscillograph.* The study of the pattern was further made by recording a

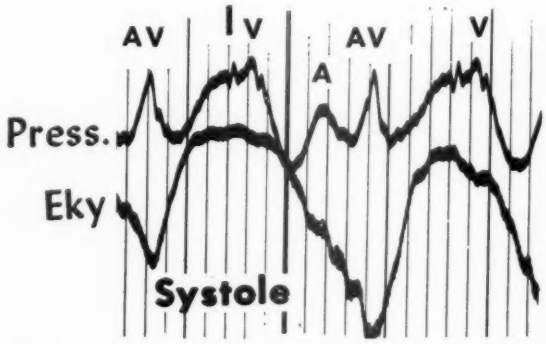

Fig. 5. Dog. Left atrial electrokymogram (below) and left atrial pressure (above) 1 week after mitral insufficiency (early plateau). (By permission, from Haring *et al.*: *Circulation Res.* 4: 381, 1956).

* Built by "Electronics for Medicine" of White Plains, New York.

TABLE I

Timing and Phase of Waves in Left Atrial Pressure (Direct Measurement) and Volume Electrokymograph Tracings

Phenomenon	Phase	Timing	Electro-kymographic tracing	Pressure tracing
Atrial contraction	Presystole	Prior to 1st heart sound. After P wave of ECG	Negative A-wave	Positive A-wave
Mitral valve closure	At beginning of ventricular systole	During first part of 1st sound. During R-S of ECG	Small positive notch (A-V wave	Small diphasic notch (A-V wave)
Opening of aortic valve and ejection	During most of ventricular systole	After 1st sound, before 2nd sound. Between S and end of T	Negative wave (systolic collapse)	Negative wave (systolic collapse)
Mitral valve opening	Early diastole	From 0.06 to 0.08 sec after 2nd sound (if present, opening snap of mitral valve). After end of T	Positive wave (V-wave)	Positive wave (V-wave)
Slow ventricular filling	Diastole	After opening snap	Negative wave (diastolic collapse)	Negative wave (diastolic collapse)

simultaneous phonocardiogram and electrocardiogram at a film speed of 100 mm/sec. Successive tracings were taken from the needle and from a polyethylene catheter (PE 50) introduced into it.

The *electrokymogram* was recorded by means of a Sanborn electrokymograph and a Stethocardiette, together with a phonocardiogram for timing. The usual rules were followed, as previously described.[16] The LA EKY was usually recorded in the sitting position, within 24 hours from the recording of pressure.

The diagnosis was based: (1) on clinical, roentgenologic, and graphic data; (2) on data of catheterization with special regard to the existence of a diastolic gradient; (3) on surgical data (eight cases) or autopsy evidence (one case).

General Criteria of Interpretation of a Pressure Tracing

(1) evidence of mitral stenosis

The existence of a diastolic gradient has been accepted as evidence of mitral obstruction. However, there is no general agreement on the criteria for its evaluation. Our measurements were based on the following criteria: (a) patient at rest; (b) evaluation during one (or possibly more) pullback maneuver which insures the same conditions and degree of amplification;* (c) measurement of the diastolic pressure both in the atrium and ventricle at one-half of diastole (if there is atrial fibrillation) or just prior to the atrial contraction (in cases with sinus rhythm); (d) average of at least 10 cycles for the atrium and the ventricle during normal respiration.

(2) evidence of mitral regurgitation

As pointed out before, the left atrial pressure tracing of normal individuals shows a gentle depression during ventricular systole (Fig. 6A). As this is due to lowering of the A-V floor by left ventricular pull, it is possible that rigidity of the mitral leaflets might prevent this depression, either partly or totally. On the

* During a pullback, the zero line will change slightly because the tip of the catheter will rise across the mitral valve. This, however, is less than 1 mm Hg.

TABLE II

Correlation of Pressure and Electrokymogram with Levels of Left Atrial Pressure

	No.	Name	Final diagnosis	Mid-diastolic gradient mm Hg	Mean systolic elevation mm Hg	Rhythm	Pressure pattern	Electro-kymographic pattern	Observations at surgery or autopsy
Normal	1	G. J.	Normal	0	0	Sinus	Normal	Normal	
	2	C. D.	Normal	0	0	Sinus	Giant A	Giant A	(Postoperative)
Mitral stenosis	3	P. A.	Mitral stenosis	19	2	Sinus	Giant A	Late plateau	No regurgitant jet felt
	4	S. L.	Mitral stenosis	16	2	Sinus	Giant A	Normal	
	5	L. S.	Mitral stenosis	15	1	Sinus	Giant A	Normal (giant A)	
	6	H. E.	Mitral stenosis. Aortic stenosis	17	1	Sinus	Normal	Small late plateau	No regurgitant jet felt
Mitral stenosis and insufficency	7	M. R.	Mitral stenosis and minimal insufficiency	28	7	Sinus	Intermediate	Small late plateau	Minimal jet felt
	8	D. S.	Mitral stenosis and minimal insufficiency	16	5	Sinus	Intermediate	Late plateau	No regurgitant jet felt
	9	L. W.	Mitral stenosis (moderate) and minimal insufficiency	8–13	3	Atrial fibrillation	Intermediate (small plateau)	Late plateau	Regurgitant jet felt by surgeon
	10	R. M.	Mitral stenosis (moderate) and minimal insufficiency	8	3	Atrial fibrillation	Intermediate (small plateau)	Late plateau	
	11	M. C.	Mitral stenosis (moderate) and insufficiency (moderate)	10	10	Atrial fibrillation	Plateau (medium)	Late plateau	No regurgitant jet felt by surgeon
	12	B. G.	Mitral stenosis (severe) and insufficiency (moderate)	18	11.5	Atrial fibrillation	Plateau (medium)	Late plateau	No regurgitant jet felt by surgeon
	13	B. A.	Mitral stenosis (severe) and insufficiency (moderate)	23	11.5	Atrial fibrillation	Plateau (medium) plus small V	Late plateau	Minimal jet felt by surgeon
Mitral insufficiency	14	C. S.	Mitral insufficiency (severe). Aortic insufficiency	0	22 (maximum 72)	Atrial fibrillation	Giant I (insufficiency wave)	Giant I	Died 8 months later. Moderate aortic insufficiency; severe mitral insufficiency, minimal aortic stenosis
	15	D. D.	Mitral insufficiency (severe)	1	14 (maximum 49)	Atrial fibrillation	Giant I	Giant I	
	16	M. G.	Mitral insufficiency (severe)	4	21 (maximum 44)	Atrial fibrillation	Giant I	Early plateau	
	17	W. L.	Mitral insufficiency (moderate)	5	8	Atrial fibrillation	Giant I–V	Giant I–V	

other hand, any increase in pressure prior to the second sound is definitely due to blood flow into the left atrium. It has been said that, in patients with severe mitral stenosis, a greater flow of blood is coming from the pulmonary veins. However, this would not account for more than a minimal rise in pressure and would be revealed by an oblique line. On the other hand, whenever such an increase is present and the diastolic gradient is absent or moderate, it is apparent that the blood flowing into the atrium is coming also from the ventricle. As various patterns were encountered, it was decided to evaluate the mean systolic elevation of pressure

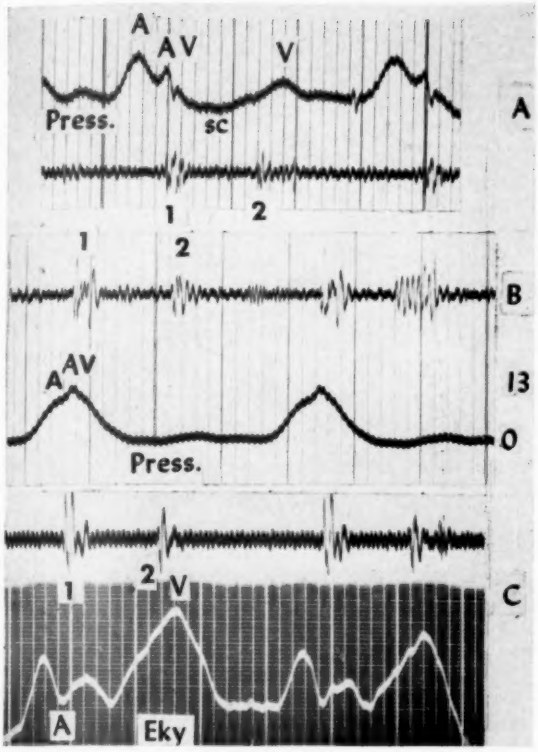

Fig. 6. A. Normal left atrial pressure pattern (Case 1—normal subject). B. Normal left atrial pressure with giant A-wave (Case 2). C. Normal left atrial electrokymogram with giant A-wave (Case 2). Case 2 was studied after mitral commissurotomy.

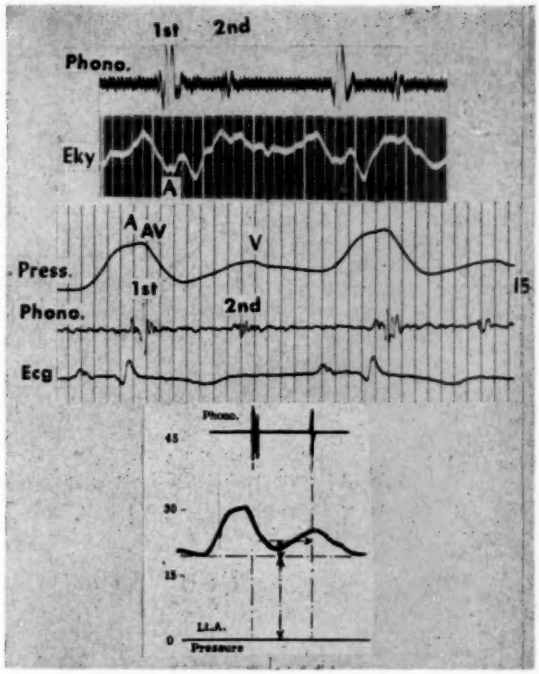

Fig. 7. Left atrial electrokymogram (above) and pressure tracing (below). Giant A-waves in both tracings. (Case 5—mitral stenosis). The electrokymogram tracing is recorded at 75 mm/sec, the pressure tracing is recorded at 100 mm/sec. The heart sounds give the timing.

in millimeters by a planimetric method and to accept it as a measure of mitral regurgitation.

Results

(1) *Normal:* Two patients presented a normal level of left atrial pressure. One of them had an aortic systolic murmur and no abnormality was found (Fig. 6A). The other had been previously operated on for mitral stenosis and presented a prominent A-wave, probably due to the still existing left atrial hypertrophy (Fig. 6B). In both cases, the electrokymographic pattern was normal and equivalent to that of the pressure tracing (Tables II and III) (Fig. 6C).

(2) *Pure Mitral Stenosis:* Mitral stenosis was admitted in four cases on the basis of a high diastolic gradient of from 15 to 19 mm Hg (Tables II and III). As the mean systolic elevation was from 1 to 2 mm of pressure, no significant insufficiency was admitted. All four

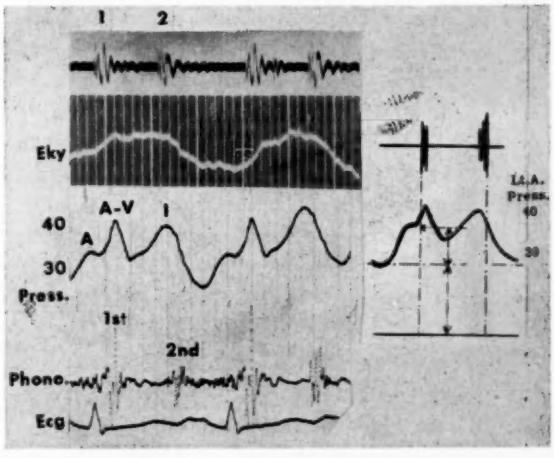

Fig. 8. Left atrial elektrokymogram (above) and pressure tracing (below). High A-wave and A-V notch; preserved systolic collapse followed by a tall I-wave, much higher than A. The electrokymogram shows a late-plateau pattern. (Case 7—predominant stenosis, minimal insufficiency). For timing, see Fig. 7.

TABLE III
Hemodynamic Findings

		Age	Sex	Height (cm)	Weight (kg)	Body Surface (m^2)	O_2 consumption (cc/min)	O_2 consumption index (cc/min/m^2)	O_2 Volume (%)			Cardiac output (l/min)	Cardiac index (l/min/m^2)
									Brachial artery or left atrium	Pulmonary artery	A-V difference		
Normal	1. G. J.	37	M.	176	77.5	1.93	—	—	—	—	—	—	—
	2. C. D.	40	F.	166	61	1.67	195	117	15.8	10.7	5.1	3.81	2.28
Pure mitral stenosis	3. P. A.	37	F.	168	74	1.84	—	—	—	—	—	—	—
	4. S. L.	30	F.	154	52.5	1.48	—	—	—	—	—	—	—
	5. L. S.	43	M.	167	72	1.82	217	119	14.8	8.5	6.3	3.44	1.89
	6. H. E.	42	M.	178	72	1.89	—	—	—	—	—	—	—
Mitral stenosis and insufficiency	7. M. R.	27	F.	168	47	1.48	264	178	14.7	7.5	7.2	3.66	2.48
	8. D. S.	40	F.	167	55	1.60	—	—	—	—	—	—	—
	9. L. W.	46	M.	182	70	1.89	237	125	15.7	10.3	5.4	4.39	2.32
	10. R. M.	30	F.	161	60	1.63	220	135	17.0	11.3	5.7	3.86	2.37
	11. M. C.	35	F.	156	63	1.62	212	131	15.2	10.5	4.7	4.52	2.78
	12. B. G.	40	F.	162	54	1.55	243	157	17.1	—	—	—	—
	13. B. A.	41	F.	158	45.5	1.43	—	—	14.2	—	—	—	—
Mitral insufficiency	14. C. S.	36	M.	176	59.5	1.72	259	150	16.2	10.3	5.9	4.40	2.56
	15. D. D.	37	F.	157	57	1.56	—	—	16.5	—	—	—	—
	16. M. G.	39	F.	150	39.5	1.29	248	192	16.7	6.2	10.5	2.36	1.83
	17. W. L.	47	F.	162	74	1.77	232	132	12.9	5.2	7.7	3.07	1.70

* Diastolic gradient left atrium-left ventricle

† The calculated functional mitral valvular areas (in Cases 7, 9, 10, and 11) are smaller than the actual area because of mitral insufficiency. Actual mitral valvular flow is larger than calculated mitral valvular flow which assumes *no* insufficiency.

cases had sinus rhythm. The pattern of pressure revealed a giant A-wave in three out of four cases, while V was always lower than A (Fig. 7). The electrokymographic pattern consisted of a giant A-wave in one case, a normal pattern in two (Fig. 7) and a plateau pattern in two cases (late plateau) during ventricular systole. No regurgitant jet was felt by the surgeon in the two operated cases.

(3) *Mitral Stenosis and Insufficiency:* This group of cases includes seven patients (Tables II and III). Mitral stenosis varied from moderate to severe, as proved by diastolic gradients of from 8 to 28 mm Hg. The mean systolic elevation was appreciable in all of them. It was slight in four (3 to 7 mm, Cases 7 to 10), and moderate in three (10 to 11.5 mm, Cases 11 to 13). Five out of seven cases had atrial fibrillation while two (Cases 7 and 8) had sinus rhythm. The left atrial pressure patterns revealed either an intermediate type or a plateau. The term "intermediate type" was characterized by a high A-V wave during the first sound, then a drop, then a rapid rise, if the bottom of the systolic drop was still higher than the left atrial middiastolic pressure (Fig. 8, 9). It is worthy of mention that, in Cases 7, 11, and 13, following a grossly plateau-like pattern, there was a drop of the curve before the 2nd sound instead of after it. In Case 13, there was the same phenomenon and then a small V-wave was present as a notch on the descending branch of the plateau (Fig. 10). In all seven cases, the electrokymogram presented the pattern called late-plateau (Fig. 8, 9, 10). A moderate regurgitant jet was felt by the surgeon in three operated cases, not in three others.

(4) *Pure Mitral Insufficiency:* No mitral stenosis was admitted in four cases because the diastolic gradient was 5 mm or less. In all of them,

TABLE III—continued
Hemodynamic Findings

Pressures (mm Hg)															Mitral valve		Functional mitral valvular areas† (cm²)
Pulmonary artery				Right atrium	Brachial artery		Left ventricle		Left atrium						Evidence of stenosis*	Evidence of insufficiency**	
Systolic	Diastolic	Mean	Mean wedged	Mean	Systolic	Diastolic	Systolic	Diastolic	Diastolic	A	A-V	Systolic mean	V	Mean			
—	—	—	—	—	100	64	100	8–9	8	15	12.5	8	10	10	0	1	—
14	4	10	7	4	98	64	95	6	6	13	13	6	7	7	0	0	—
—	—	—	—	—	94	56	94	6	25	35	34	27	30	27	19	2	—
—	—	—	—	—	106	58	106	6‡	22	30	33	23	25	25	16	2	—
47	27	36	20	6	116	80	116	6	21	34	34	22	26	24	15	1	0.81
115	60	84	—	—	97	57	147	12	29	32	31	30	34	30	17	1	—
116	62	85	34	6	110	70	106	4	32	36	43	39	45	38	28	7	0.72
—	—	—	—	—	110	74	110	4.5	20	25	28	25	27	23	16	5	—
80	31	48	—	10–14	116	66	106	6–11	19	—	20	22	24	21	8–13	3	0.86–1.15
35§	—	—	—	7	112	68	114	4–7	12	—	16	15	16	14	8	3	1.15
33	22	28	22	5	100	72	92	2–9	19	—	25	29	30	24	10	10	1.31
—	—	—	—	—	110	68	110	8	26	—	37	37.5	39	31	18	11.5	—
—	—	—	—	—	110	76	110	4	27	—	37	38	40	32	23	11	—
80	34	50	—	1	125	57	106	16	16	—	19	38	72	29	0	22	—
—	—	—	—	—	98	56	90	20	21	—	31	36	49	30	1	15	—
81	48	59	—	20	150	90	150	10‡	14	—	27	35	44	22	4	21	—
43	34	38	14	5	120	74	120	7–9	14	—	16	22	29	17	5	8	—

** Rise of LA pressure in systole (LA systolic mean minus LA diastolic.)
‡ Assumed left ventricular diastolic pressure.
§ Right ventricular systolic pressure.

there was evidence of severe regurgitation with a mean systolic elevation which varied from 8 (moderate) to 22 mm (severe) (Tables II and III). The severity of the regurgitation was further revealed by the peak of the regurgitant wave which reached 44 mm (Case 16), 49 mm (Case 15), and 72 mm (Case 14). The pattern of pressure revealed a peaked, grossly triangular wave in late systole (Fig. 11). It is important to note, that, in three cases out of four, the peak of the wave coincided with the 2nd aortic sound and thus preceded the V-wave while, in the fourth, it followed the second sound by 0.08 sec. For this reason, this wave was called I (insufficiency) wave in the former three cases, I-V (insufficiency wave plus V-wave) in the last case. The electrokymogram revealed a pattern which was similar to that of pressure in three out of four cases (Fig. 11) while it revealed a plateau pattern in the other (Case 16). One patient died eight months after our study. Autopsy confirmed severe mitral in sufficiency and no stenosis.

Discussion

The purpose of this investigation was manifold. It included:

(a) an accurate study of the pressure patterns recorded in the left atrium through direct puncture of this chamber;
(b) a comparison of these patterns with simultaneously recorded sound tracings and electrocardiograms (for timing);
(c) a comparison of these patterns with those recorded through a roentgenologic method (electrokymogram); and,
(d) a final evaluation of the value of the various methods.

Diastolic Gradient: The study of the diastolic pressure gradient between left ventricle and left atrium was done according to previous studies of

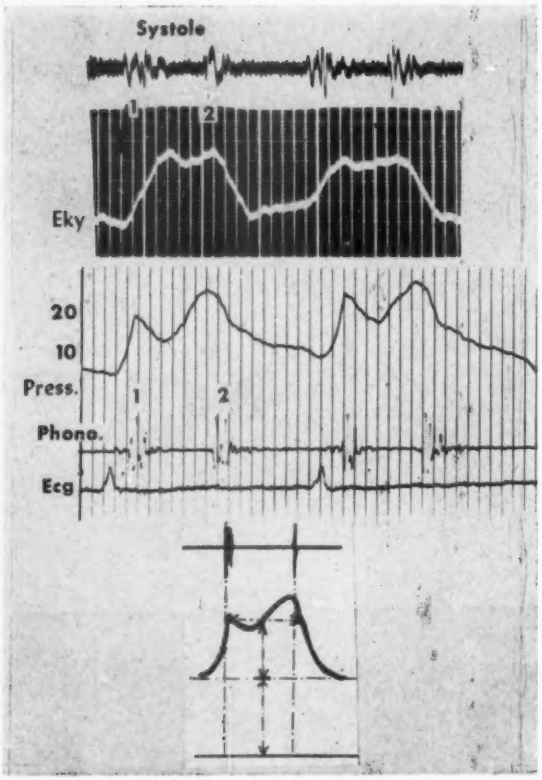

Fig. 9. Left atrial electrokymogram (above) and pressure tracing (below). Plateau pattern in both, even though they still show minor evidence of the systolic collapse. (Case 11—moderate insufficiency and stenosis, atrial fibrillation). The electrokymogram has been photographically enlarged so that systole has the same duration as in the pressure tracing.

Bjoerk, Soulié, Moscovitz, Wood, Fisher, and others. Special care was taken in the measurement of this gradient (see "general criteria").

Systolic Elevation: Considerable confusion exists in the literature in regard to the evidence for mitral regurgitation. It has been stated that a normal raising of the mitral leaflets might account for a rise in pressure. From a physiologic standpoint, this is possible only during the first part of the first sound (A-V notch) and would be decreased by the rigidity which is inherent in mitral stenosis. It has also been stated that "the high pressure of the pulmonary veins due to mitral stenosis would cause a high V-wave which could be confused with the high wave of mitral insufficiency." It is obvious that an accurate study of the pressure pattern of insufficiency should be made first in cases without stenosis. In these cases, we found a high triangular wave in late systole. In three cases out of four, its peak was prior to or coincident with the second sound. Therefore, it was not a V-wave but a new, late-systolic wave due to regurgitation, which we called I-wave. Only in the fourth case did the peak coincide with mitral opening. However, the gradual rise of pressure during ejection showed that there was regurgitation and that there was a fusion between the pathologic I-wave and the subsequent normal V-wave (Giant I-V wave).

Theoretically, mitral regurgitation should cause a plateau pattern in the left atrium. Our experiments showed that such was the case only in extremely severe regurgitation. Moderate regurgitation caused a gradual rise of pressure with one peak at the second sound (I) and a second peak some time later (V) (Fig. 5). This observation coincides with previous studies of

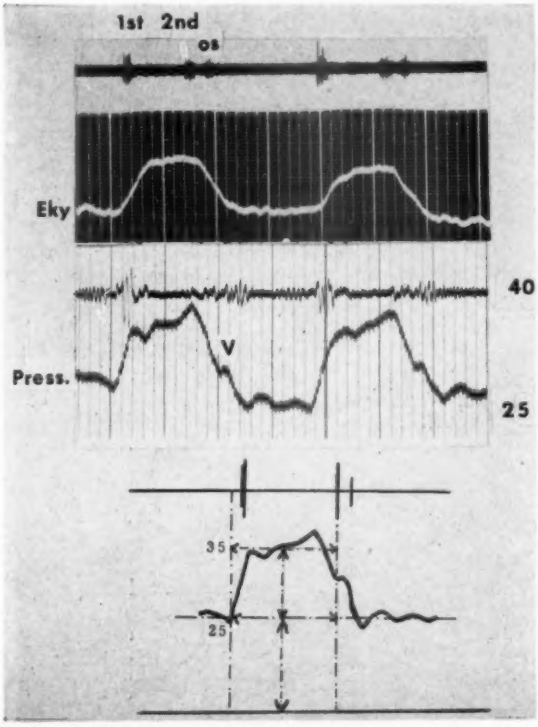

Fig. 10. Left atrial electrokymogram (upper tracing) and pressure (lower tracing). Both are timed by phonocardiograms. Plateau-like pattern. The V-wave is visible on the descending branch of the plateau in the pressure tracing. Severe stenosis and moderate insufficiency of the mitral valve. Atrial fibrillation (Case 13). Duration of systole similar in both tracings.

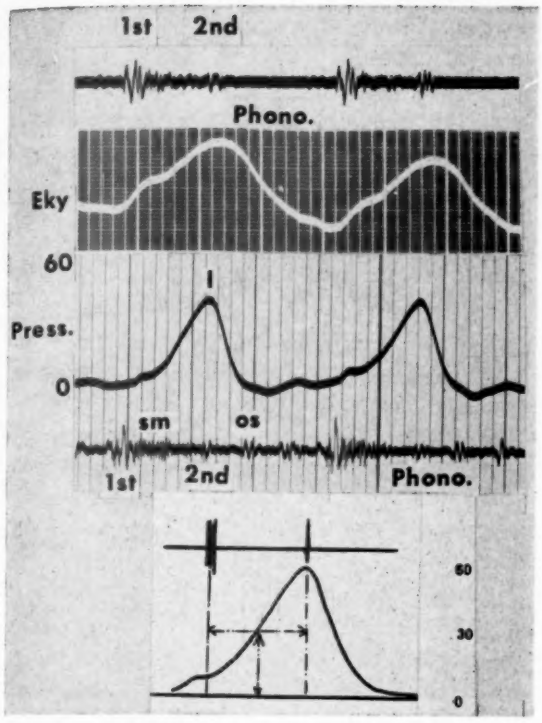

Fig. 11. Left atrial electrokymogram (upper tracing) and pressure (lower tracing). Both are timed by phonocardiograms. Giant I-wave with peak at the 2nd sound. Pure insufficiency, atrial fibrillation (Case 14).

Wiggers and Feil.[15] One possible explanation for this graduality of rise is that the elastic wall of the left atrium distends with the regurgitant jet and absorbs part of the pressure rise in early systole. This was actually proved in one animal experiment (Fig. 5) and in one of our clinical cases (Case 16) where the electrokymogram revealed a plateau-like wave while the pressure pattern was that of a gradual rise.

Typical Patterns: The study of pressure pulses revealed certain typical patterns:

(1) In pure mitral stenosis, either a giant A-wave (sinus rhythm) or no abnormality of the pattern.

(2) In pure mitral insufficiency, the occurrence of a triangular, late-systolic wave (I-wave) which only occasionally fuses with the following (early-diastolic) V-wave.

(3) In mitral stenosis plus insufficiency, an entirely new pattern was found. This consisted of a plateau-like wave during ventricular systole. Several variations of this main pattern were found, as follows:

(a) A high A-V notch followed by a drop; this, however, fails to reach the diastolic level. This was called *an intermediate pattern* and interpreted as evidence of minimal insufficiency in the presence of severe stenosis.

(b) A giant A-wave. After this, the pressure fails to return to the diastolic level but stays high and fuses with the A-V notch, then drops without reaching the baseline. This also was called *an intermediate pattern* and interpreted like that of (1).

(c) Either with sinus rhythm or atrial fibrillation, there is a plateau-like wave during ventricular systole. This may be either with a flat top or with an oblique line. The end of the plateau may be before the second sound, at the second sound, or after the second sound. This pattern was called *plateau pattern* and interpreted as evidence of moderate

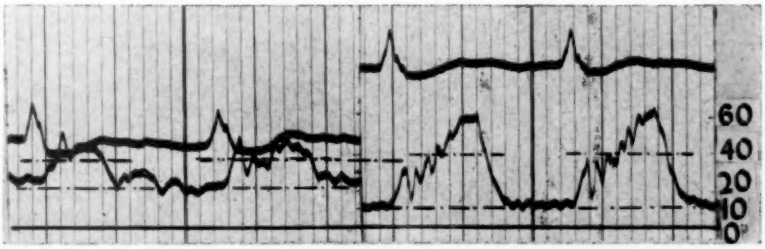

Fig. 12. Pressure tracing of left atrium measured on the operating table before (A) and after (B) commissurotomy. The plateau pattern existing prior to operation becomes taller and has an earlier and steeper rise after surgery (increase of regurgitation). While the pattern before surgery was a typical plateau, that after surgery has a late-systolic elevation which is similar to that of pure insufficiency. The vibrations of the murmur are visible in the pressure tracing after commissurotomy.

insufficiency in the presence of moderate to severe stenosis. The drop of pressure starts before the second sound when pressure is very high in the atrium; at the second sound in most cases; and at the time of the V-wave in a few cases with minimal stenosis. Thus, the end of the plateau behaves like an I or an I-V wave. Our interpretation is confirmed by the changes of the plateau pattern occurring immediately after surgery (Fig. 12).

We have wondered about the reason why pure insufficiency should give a late-systolic, triangular wave while insufficiency plus stenosis should give a plateau-like pattern. One possible explanation is that the existence of mitral stenosis, with its high diastolic pressure, keeps the atrial walls under a state of permanent tension. Thus, if regurgitation occurs, a more accurate reproduction of ventricular pressure takes place in the atrium.

Electrokymogram and Pressure Tracings: On the whole, a remarkable coincidence between the two types of tracings was found. The two cases with normal mitral valve had a perfect coincidence between electrokymogram and pressure tracing. In two of the four cases of pure stenosis the electrokymographic pattern was grossly normal (not revealing insufficiency) while in the other two, some evidence of insufficiency was found. One could still wonder whether sedation and the prone position did not prevent a minimal regurgitation in those two cases at the time of pressure recording. Out of seven cases of mitral stenosis plus insufficiency, a plateau-like pattern of various degree was found, by electrokymogram and pressure patterns, in all. Thus, no contrast between the two methods resulted. Out of four cases with pure regurgitation, a giant, triangular, I-wave (or I-V wave) was found by pressure pattern studies in all, by EKY in three, while the fourth had an early plateau. This, again, reveals a remarkable coincidence between the two methods. In Case 16, the existence of a plateau by electrokymographic border tracing (equivalent to a volume tracing) in contrast with a slower rise of pressure can be explained by the severe distention of the atrial walls decreasing the rapidity of the rise of pressure. On the other hand, the other three cases had a similar slow rise both in pressure and electrokymogram (volume) tracings. This can be explained only in one way: some means of compensation (left ventricular muscular contraction?) which prevents excessive regurgitation during most of ventricular systole and allows the pressure to rise slowly.

Summary and Conclusions

A comparative study of left atrial pressure tracings and left atrial electrokymograms was made in 17 cases. The obtained data were correlated with the clinical findings, the electrocardiographic and phonocardiographic tracings, and the roentgenologic picture. In eight cases, the findings of the surgeon and ih one, autopsy findings, were also obtained.

The degree of mitral stenosis was evaluated on the basis of the *diastolic gradient* between left ventricle and left atrium. Technical details concerning the measurement of this gradient were presented and discussed. It was tentatively decided to admit moderate stenosis if the gradient was between 7 and 12 mm Hg, severe stenosis if it was above 12 mm.

A careful study of the pressure pattern of the left atrium in normal animals and normal humans reveals that, during ejection, a drop of pressure takes place. Therefore, whenever the pressure rose in the left atrium during ejection, it was admitted that there was mitral regurgitation. Various opinions to the contrary were refuted. A possible factor changing the slope of pressure was admitted, i.e., an elastic distention of the atrial walls, maximal in "pure" insufficiency (which has a normal diastolic tension), slight or inexistent in mitral stenosis with insufficiency (which has a high diastolic tension). From this was evolved the concept of the *mean systolic elevation*. Technical details concerning it were presented.

Three main patterns were observed in mitral patients:

(1) Normal pattern or giant A-wave was found in pure mitral stenosis.

(2) A plateau pattern was found in cases with mitral stenosis and insufficiency. Data indicating that the plateau was due to transmission of left ventricular pressure

to the left atrium (i.e., mitral regurgitation) were presented.

(3) A late-systolic wave was found in pure mitral insufficiency. Reasons why this wave should be called I-wave (insufficiency wave) are given. This wave may occasionally fuse with the normal V-wave or may have a peak before the end of systole.

A comparison of the electrokymographic patterns with those of left atrial pressure revealed that there was a substantial coincidence between the two in 13 out of 17 cases. In two other cases, the electrokymogram revealed a plateau pattern while the pressure tracing did not. This could be explained by an elastic distention of the atrial walls causing a slower rise in pressure. In two cases, on the contrary, technical error was considered.

It was concluded that electrokymography supplied significant data in cases of *mitral insufficiency and stenosis* even though it would not permit to quantitate the insufficiency. The degree of stenosis of these cases could be guessed though study of the pattern (late plateau) but not accurately evaluated.

In *pure mitral insufficiency*, the electrokymogram can give either vague information (early end of systolic collapse by I-wave) or show a typical plateau pattern (early plateau).

In *pure mitral stenosis*, the electrokymograms cannot supply significant data having diagnostic value but may help in ruling out a concomitant insufficiency.

On the basis of the above, it was concluded that a correctly recorded and interpreted left atrial pressure pattern is the most useful and significant laboratory finding in cases of mitral valve disease. On the other hand, considering the ease and harmlessness of electrokymographic recordings, it was concluded that they should be taken systematically in all mitral valve patients. Their most significant data seem to be obtained in mitral stenosis with concomitant insufficiency. However, considering the limited number of cases having pure insufficiency observed in this study and previous findings obtained in mitral patients after surgery, it is possible that this conclusion should be revised.

JANUARY, 1958

ACKNOWLEDGMENTS

We wish to acknowledge the collaboration of Drs. C. Aravanis and M. R. Testelli, who worked in the catheterization team during this study.

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Mitral Stenosis—New Concept of Correction by Rehinging of the Septal Leaflet*

Neo-Strophingic Mobilization

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COMPLETE mobilization of the stenotic mitral valve has been achieved in the past only in those few individuals in whom the leaflets have become but slightly deformed and lightly cross-adherent, the chordopapillary supports remaining relatively free and flexible. Such patients make up no more than 10 to 12 per cent of those who seek surgical aid for mitral stenosis. The remaining 90 per cent or so of patients have what amounts pathologically to a fibrous or fibrocalcific stricture of the left atrioventricular passageway (Fig. 1, A, B).

The benefit initially achieved by commissurotomy in these patients who have advanced pathologic changes in the valve frequency has been of limited degree. This is not surprising when one considers that the type of mobilization usually obtained is that which is represented in Figure 2, A, B. Unless a considerable amount of residual *flexibility* persists in the leaflets and in the subvalvular supporting structures, relatively little mobility and even less function will be restored to the valve. In 67 per cent of our first 1,200 patients operated from the left side, it was possible to open only one commissure.[1]

The ultimate result is compromised further if a calcific bridge or fibrous thickening is permitted to remain intact across the posteromedial commissure (Fig. 3).

In the standard operation, designated "mitral commissurotomy"[2] and in the identical procedures called "valvulotomy,"[3] "valvulopasty,"[4] and "valvotomy,"[5] the primary attempt has been to "lengthen" the mitral slit in a linear fashion as first suggested by Sir Lauder Brunton[6] in 1902 (See Fig. 2). Improvements in the anatomic mobilization of the various elements of the valve mechanism have been made possible by the recognition of the importance of freeing any subvalvular cross-fusion of the chordopapillary muscles,[7,8] by use of the bare-finger technic,[9] by the employment of special instruments,[8] by approaching the valve from the opposite side of the operating table (but still through the left auricular appendage) and by the use of the opposite (left) index finger also inserted through the left auricular appendage.[1]

However, the very real risk of producing a serious grade of regurgitation, especially when attempting instrumentally to divide the "posteromedial" commissure, the danger of dislodgement of calcific fragments which frequently may be found encrusted upon the valve orifice, and the many inherent technical disadvantages associated with the approach to the mitral valve by way of the left auricular appendage, have contributed to a philosophic acceptance by nearly all cardiac surgeons of a relatively limited degree of valvular mobilization in most cases.

The advent of the right-sided approach to

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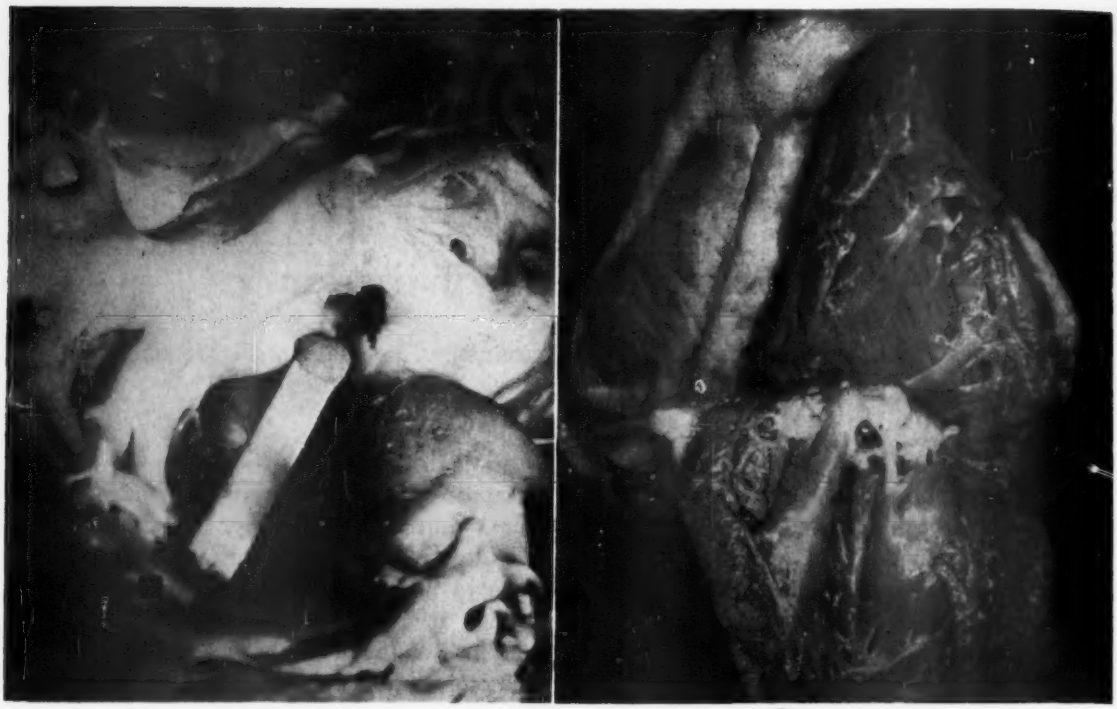

A B

Fig. 1. A. Photograph of an extremely stenosed mitral valve which really has been converted into a fibrous stricture. (Bailey, C. P., Lacy, M. M., and Harris, J. S. C.: The surgical treatment of acquired heart disease. *Surg. Clinics N. America* 31: 4, 1951. Courtesy of W. B. Saunders Co., Philadelphia.) B. Equally stenosed mitral valve which has become converted into a fibrocalcific stricture. (Bailey, C. P.: *Surgery of the Heart* 1st ed., 1955, p. 515. Courtesy of Lea and Febiger, Philadelphia.)

the mitral valve,[10] in 1954, and its subsequent technical improvements[11,12] have provided us with a much more advantageous method of attack upon the stenotic mitral valve.[13] Uni-commissural separation of the valve has become a rarity, and bicommissural mobilization the rule (95 per cent). However, for some time we continued to be restricted mentally by the

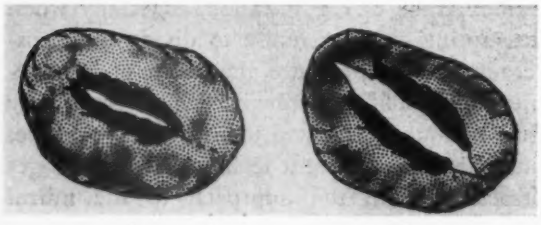

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Fig. 2. Classical concept of a stenosed mitral valve and its surgical mobilization. A. Representation of stenosed valve. The black shading indicates marginal scarring of the leaflets. B. Linear elongation of the diminutive valve slit. Complete division of the scar tissue was presumed to be capable of restoring a normal type of "flutter-valve" movement to the leaflets. (O'Neill, T. J., Glover, R. P., and Bailey, C. P.: Commissurotomy for mitral stenosis, *J. Internat. Coll. Surgeons* 13: 4, April, 1950, p. 359. Courtesy of J. International College of Surgeons.)

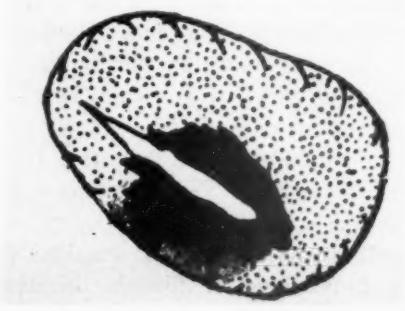


Fig. 3. Actual surgical accomplishment in the majority of cases of mitral stenosis since only the anterolateral commissure is opened routinely. Frequently this procedure leaves a dense horse shoe-like fibrous or calcific bridge at the posteromedial commissure which significantly restricts the potential of valve movement. Note extent of fibrosis of the mural leaflet which is characteristic in mitral stenosis.

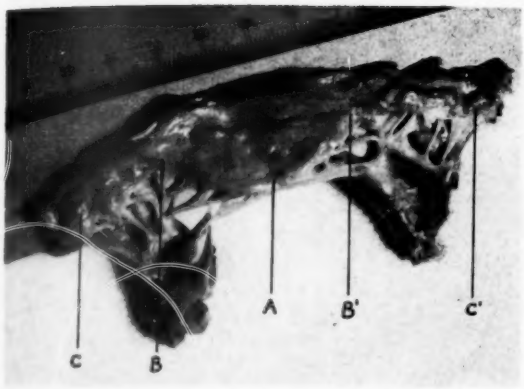


Fig. 4. Figure of excised two-leafed mitral valve ribbon (mural cusp C-C′ having been divided). A—roughly triangular septal leaflet. B-B′—junctional tissue. (Bailey, C. P.: *Surgery of the Heart*, 1st ed., 1955, p. 492. Courtesy of Lea and Febiger, Philadelphia.)

original concepts and practices of the former type of surgery from the left side, so that the actually accomplished operative procedure remained basically but an improved mitral "commissurotomy."

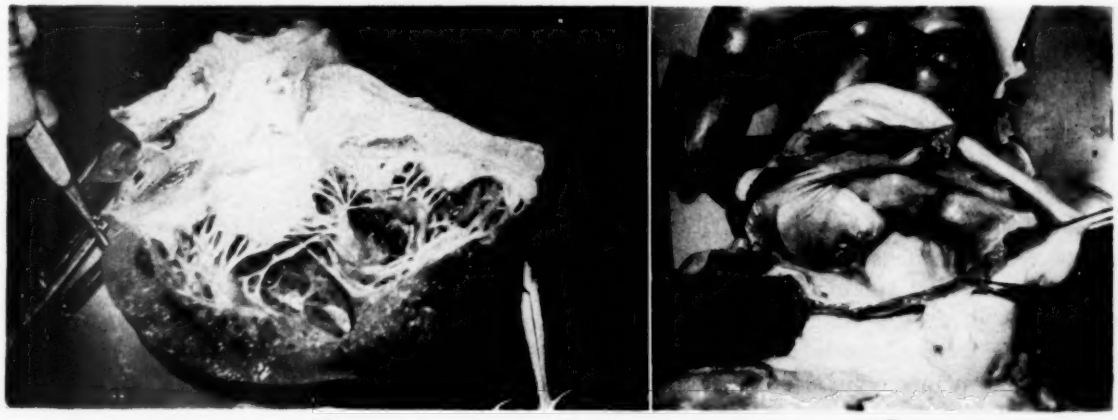
Finally, as a combined result of our enhanced facility in the enlarging of the valve by the right-sided method, and an ever-increasing desire to produce a type of valve separation which would be both less likely to create insufficiency and less subject to ultimate obliteration by restenosis, a new concept and technic of mitral mobilization was conceived. The term "reconstitution" has been chosen to designate this operation because it denotes a more complete restitution of mitral valve function than is implied in the various procedures known as "commissurotomy," "valvulotomy," "valvuloplasty," or "valvotomy."

In essence, valve function is restored by completely mobilizing the partially flexible septal leaflet from the remainder of the valve mechanism so that it is enabled to move freely as on a *new hinge*. This has been described as "neostrophingic mobilization of the septal leaflet" (Gr. neo—new, strophinx—hinge). This objective differs widely in concept from that of the older operation which was designed merely to *lengthen the valve slit*.

The Anatomic Basis of Neo-Strophingic Mobilization

The actual valve substance is a thin continuous ribbonlike membrane which arises from the left atrioventricular annulus fibrosus. It varies considerably in width and is divided into two major leaflets called respectively the septal or aortic, and the mural or ventricular, which are joined at either extremity by what Chiechi[14] calls "junctional tissue" (Fig. 4).

The septal or greater leaflet is roughly triangular in outline (Fig. 4). Its total area is more than one-half of the surface of all the valve ribbon. Its *apicobasal* length (from the center of its free edge to the center of its base on the annulus) is two or three times the apicobasal length of the mural leaflet.



A B

Fig. 5. A. Human mitral valve with two accessory or commissural leaflets. B. Bovine heart showing characteristic quadricuspid structure of mitral valve. (Bailey, C. P.: *Surgery of the Heart*, 1st ed., 1955, p. 492. Courtesy of Lea and Febiger, Philadelphia.)

The latter, however, with the addition of the junctional tissue (or accessory leaflet substance), makes up a considerably larger proportion of the annular attachment of the valvular ribbon.

In some cases, the junctional tissue appears to be differentiated into additional accessory leaflets which may cause the valve to assume a quadricuspid structure similar to that in the bovine heart (Fig. 5 A, B). A considerable difference of opinion exists as to the relative incidence of multicuspid valves in the human being. Harken *et al.*[15] estimate the incidence of the quadrangular structure at 75 per cent. On the other hand, Rusted and associates[16] found one or more accessory cusps in but 5 per cent of normal mitral valves. Chiechi[17] studied 105 normal mitral valves and found the frequency of occurrence of accessory leaflets to be that shown in Table I.

TABLE I

The Frequency of Accessory Leaflets in Normal Mitral Valve (105 Hearts)*

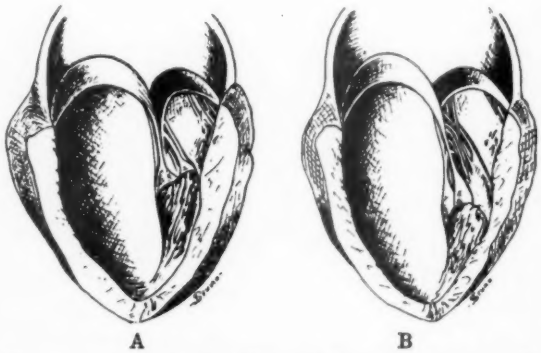
	Number of cases	%
Accessory leaflets in mitral valve	64	61
Anterior only 30 (28.6%)		
Posterior only 12 (11.5%)		
Anterior and posterior 22 (20.9%)		
No accessory leaflets	41	39
Total	105	100

* (From Chiechi, M. A., Lees, W. M., and Thompson, R.: *J. Thoracic Surg.* 32: 378, 1957).

Actually, as he pointed out subsequently, it matters little whether the junctional tissue is differentiated into accessory leaflets or not. Whatever portion of the valvular ribbon joins the two major leaflets serves chiefly to prevent regurgitation from taking place at the two extremities of the approximated major leaflet pairs at the height of ventricular systole (Fig. 6). He has further pointed out that the width of the valvular ribbon in the region of the posteromedial pole of the valve, whether differentiated into an accessory leaflet or not, is always significantly less than that at the antero-

Fig. 6. Representation of incompetence of mitral valve caused by excision (or division) of junctional tissues or accessory cusps, if present. A competent tricuspid is present on the right. This (Luciano) test is performed with the mitral leaflets floating on a water surface while a forceful jet of water is applied to the ventricular aspect of the valve in question. (Chiechi, M. A.: Functional anatomy of the mitral valve. *J. Thoracic Surg.* 32: 3, Sept., 1956, p. 391. Courtesy of C. V. Mosby Co., St. Louis.)

lateral pole (Fig. 7 A, B). From this it may be deduced that this portion of the valve is less well supported than is any other point of



A B

Fig. 7. A. Representation of the generous systolic overlap of the cusps in the region of the anterolateral (really left) extremity of the mitral valve. B. Relatively less systolic overlap of the cusps which is characteristic of the region of the posterolateral (right) pole of the valve. This least well guarded portion of the valve orifice is the first to become incompetent when generalized shrinkage of the leaflets or dilatation of the annulus takes place. (Chiechi, M. A. and Bailey, C. P.: *La Valvola Mitrale.* Il Pensiero Scientifico, Rome, 1954.

its circumference.[18–20] This concept is supported by the observation that this is the commonest (and first) site of regurgitation when the valve is incompetent, whether the cause of the insufficiency is actual shrinkage of the valve substance (from rheumatic distortion) or primary or secondary dilatation of the valve ring.[21–24]

The chordae tendinae are strong fibrous strings or cords which attach the free margins and the ventricular aspects of the major (and sometimes the minor) leaflets to the left ventricular wall either directly, as in the chordae of the third order, or indirectly, by way of the papillary muscles. The chordae of the first order are attached to the free margins of the leaflets and frequently are branched. The chordae of the second order are heavier than the previous ones, and are attached to the ventricular aspects of the cusps at a variable distance from the free edges. Both of these latter types of chordae tend to arise from the respective papillary muscles in such a fashion that at either extremity of the valve one-half of each leaflet is supported by the chordae tendinae arising from the papillary muscle assigned to the pole of the valve. This may be designated as a "yoke" or Y-type of suspension. Brock[25] has divided the major valve leaflets into central and lateral portions, and has called the arbitrary sites of division the "critical areas of tendinous insertion." In most cases, unusually heavy chordae tendinae are found to insert at either extremity of the central portion of the septal leaflet.

Chordae of the third order attach the free margin of the mural leaflet (and but rarely any other portion of the valve) directly to the ventricular wall (Fig. 8 A,B,C,D).

The papillary muscles may be single conical or pillar-like structures; they may be bifid, double, or even triple in development. In most instances, the anterolateral papillary muscle is single, while the posteromedial one more often is double or triple in formation. Although the classic "Y" type suspension of the major leaflets with a single chordopapillary structure would seem to be the one most likely to ensure ready approximation of the leaflets during ventricular systole, practical experience in the

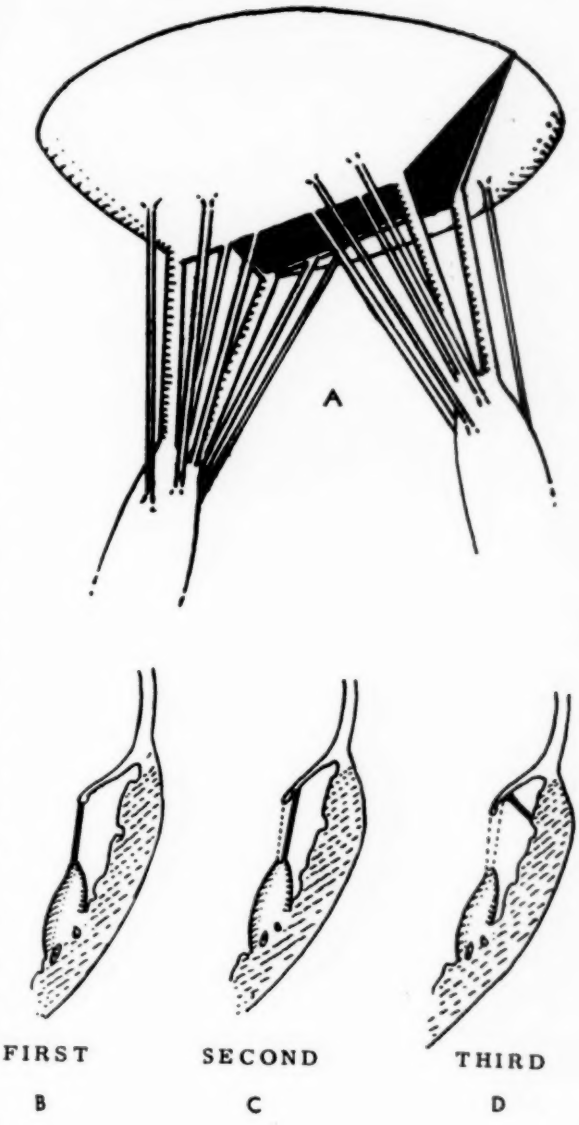


Fig. 8. A. Functional division of the mitral orifice into three parts. Note relatively heavier chordae tendineae supporting the sites of junction of the central and peripheral portions of the leaflets (Brock's line of direct tendinous support). Note typical "yoke" or Y-type of suspension.
B. Chordae of the first order which attach the free margins of both major cusps to the respective papillary muscles. C. Chordae of the second order which attach the ventricular aspects of both major cusps to the papillary muscles. D. Chordae of the third order attach the margin and close ventricular aspects of the mural leaflet (and sometimes the junctional tissue) directly to the left ventricular wall. Shortening of these cords retracts the mural leaflet toward the lateral ventricular wall, and may produce incompetence.

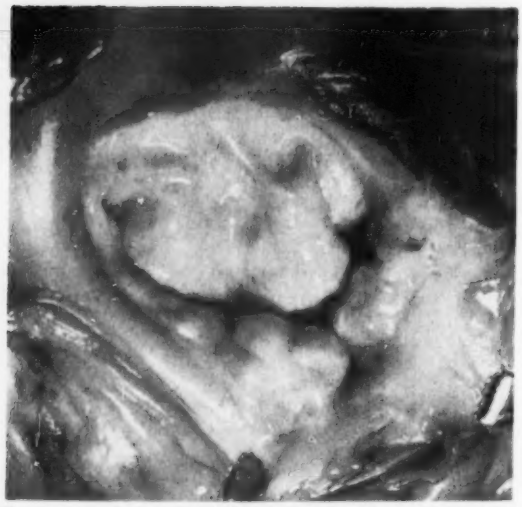


Fig. 9. Typical semicircular line of closure of the normal bicuspid mitral valve as seen with the patient in the supine position (septal leaflet above; mural leaflet below). The logical surgical ideal is reconstitution of this type of valve and orifice. (Bailey, C. P.: *Surgery of the Heart*, 1st ed., 1955, p. 491. Courtesy of Lea and Febiger, Philadelphia).

deliberate surgical splitting of these muscles seems to indicate that valvular competence is not reduced by the double type of papillary support.

Chiechi[17] has shown that the total surface area of the mitral leaflets is about twice the cross-sectional area of the atrioventricular canal. During systole the two leaflets overlap for a considerable portion of their apicobasal length. This overlap may be reduced greatly in certain disease states, actually when the apicobasal length of the leaflets is shortened by fibrotic shrinkage (usually from rheumatic disease), or relatively, due to dilatation of the ring (enlargement of the atrioventricular canal) (see Fig. 7 A,B.)

The "commissures" or sites of systolic folding of the valve ribbon at each end of the line of valve closure are impossible to demonstrate in the normal valve. It is felt that these "angles" or "commissures" really are of pathologic origin. Nevertheless, it is obvious that normally there must be points corresponding to them at which the valve folds during systole.

Commonly, it is assumed that the line of the closed human mitral valve orifice is nearly straight. In actuality, it is an arc, amounting almost to a semicircle. This configuration of the closed orifice is brought about by the previously described triangular shape of the septal leaflet, and by the consistently greater length of the annular attachment of the mural leaflet (Fig. 9). It is our feeling that surgical restoration or even exaggeration of the natural curve

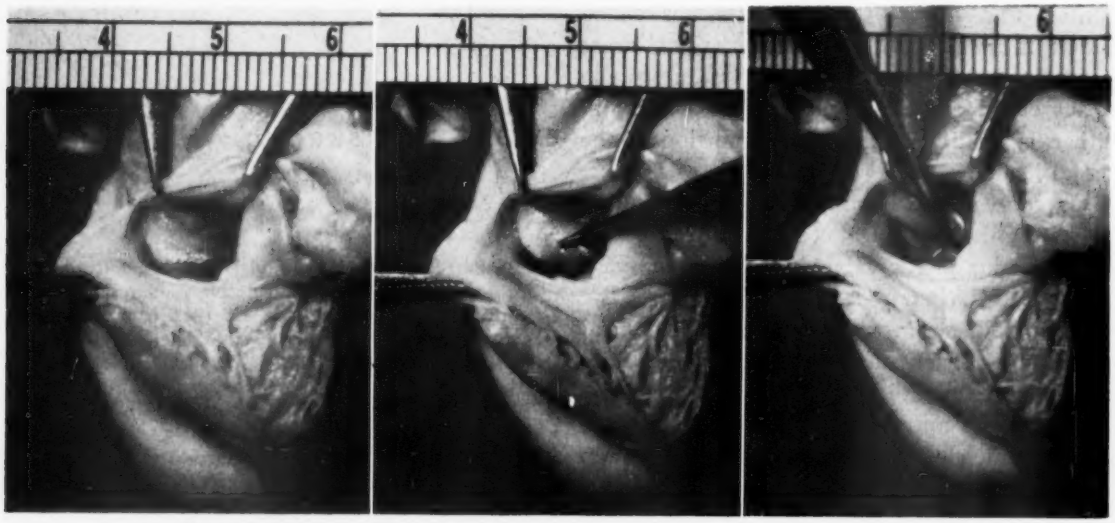


Fig. 10. Normal turtle heart showing the mitral valve in a position comparable to that in Fig. 9. Note that the sail-like septal leaflet closes against the rudimentary mural ridge like a great flap or unicuspid valve. (Note similarity to Fig. 20 A, B, C) A. Valve closed. B. Valve partly open. C. Valve open. (Note absence of mural leaflet.)

of the mitral valve are is of the utmost practical importance in the restoration of good valvular function.

While in health both major leaflets are important in the valve function, their relative importance is altered greatly in certain disease states. When the mural leaflet and the adjacent junctional tissues become significantly thickened and shrunken due to rheumatic fibrosis, restoration of their normal mobility is inconceivable. However, full mobilization of a *basally* flexible septal leaflet still may provide efficient and satisfactory valve function by enabling it to act as a great sail-like flap valve which abuts against the free margin of the shrunken mural leaflet in a manner similar to that of the major leaflet of the turtle heart (Fig. 10 A,B,C).

The Pathologic Basis for the Effectiveness of Septal Leaflet Mobilization

Rokitansky,[26] Coombs,[27] Clawson,[28] Klinge,[29] Neumann,[30] Baggenstoss,[31] and Magarey[32] have contributed most significantly to our understanding of the role of inflammation and mechanical trauma in the pathogenesis of mitral stenosis. Some comprehension of the pathologic process is essential not only in the primary alleviation of the stenosis but in the prevention of its recurrence. The "specific" rheumatic inflammatory reaction consists of the development of foci of eosinophilic staining fragmented collagen surrounded by a proliferation of peculiar, large cells (Aschoff cells) (Fig. 11). This fibrinoid degeneration of the collagen may occur as a band-like lesion covering a considerable portion of the leaflet and not infrequently is found directly beneath the endothelium of the atrial surface of the leaflet.

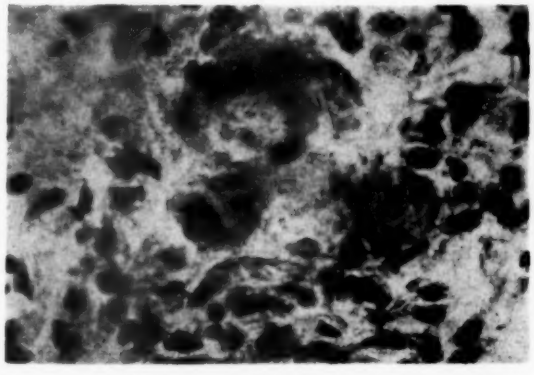


Fig. 11. Aschoff nodule in ventricular myocardium.

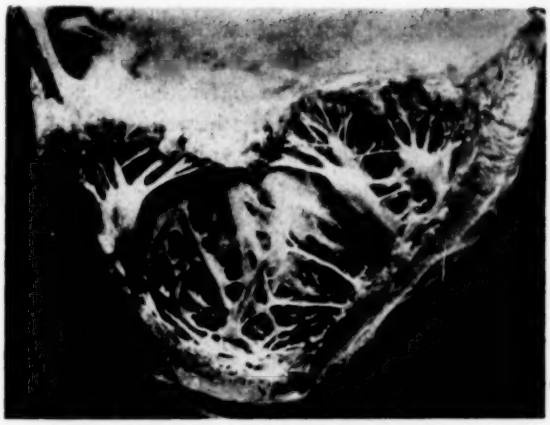


Fig. 12. A. Typical localization of rheumatic verrucose formation upon free margins and "zones of contact" of mitral cusps.

Fig. 12. B. Covering of branches and twigs of a tree with ice as seen after a freezing rain. It is believed that fibrinous exudate similarly coats the exposed surfaces of the entire valve mechanism during the course of an acute valvulitis, and perhaps in certain non-inflammatory conditions. (See Fig. 15 B.)

Tiny (1 to 3 mm diameter) translucent verrucae (vegetations) appear early on this aspect of the leaflet and are distributed chiefly over the zones of contact. This localization presumably is related to the incessantly repeated trauma to which these areas are subjected by normal valve closure (Fig. 12A).

Various opinions have been expressed as to the origin of the verracae. Originally, it was felt simply that thrombotic (fibrinous) masses from the blood accumulated upon the surface

of the inflamed valve. Since then it has been postulated that the vegetations represent disintegrated and fused proliferated cells from the superficial layers of the leaflets. This view would be suggested by the characteristic predominant localization upon the zones of maximal leaflet trauma. Still others[29,30] consider the verrucae to be extrusions of superficially located foci of fibrinoid degeneration to which may be added deposits from the blood stream. Again the trauma of valve closure is invoked to explain their localization.

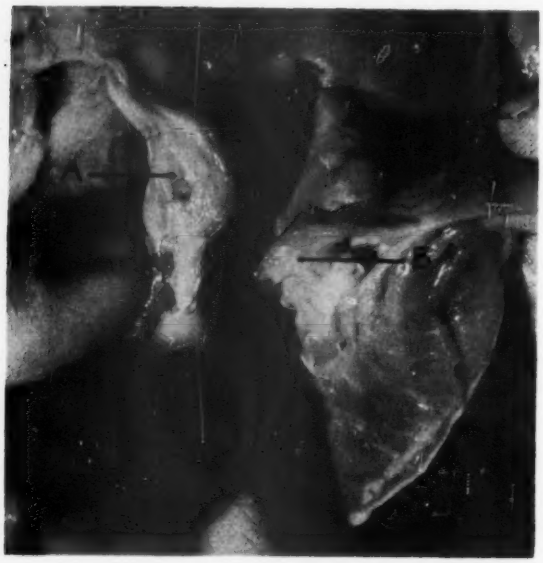


Fig. 13. Section through rheumatic mitral leaflets showing great thickening due to organization of fibrinous exudate. Note that the longer septal leaflet (A) is club-like on section, but that its basal (upper) portion is relatively uninvolved and remains thin and flexible. On the other hand, the shorter mural leaflet (B) in this specimen is totally rigid and incorporated within a mass of fibrous tissue derived from the contiguous chordae tendineae, the apex of the papillary muscle, and enveloping organized exudate. There would seem to be no practical way of restoring mobility to such distorted structures. This degraded mural leaflet now approaches in functional capacity the status of the hypoplastic mural leaflet of the mitral valve of the turtle.

Fibrinous exudate becomes deposited upon the exposed surfaces of the valve structures much like ice or snow upon the branches of a tree (Fig. 12B). Subsequent deposits may be precipitated merely by the mechanical presence of the verrucous elevations and the blood flow turbulence which they engender.[32,33]

In time, due to fibroblastic invasion and organization of both the verrucae and the exudate, a considerable thickening of the involved distal portion of the leaflets may take place, giving them a club-like appearance upon section (Fig. 13). Vascularization of the affected region of the valve may become prominent.

The important fact for surgical consideration is that the thickening of the valve leaflets begins as stated, at the free margin. This implies that although stiffened in that area, the septal leaflet, if properly hinged, could bend at its proximal flexible portion.

At the commissures, because of the incessant opening and closing of the valve, the layers of surface exudate become disturbed and heaped up much as snow is accumulated in the gutter after plows have cleared the sidewalk and the main portion of the street (Fig. 14). Eventually, fibroblasts invade these commissural masses and the ensuing fibrous transformation results in a limited degree of cross-fusion of the extremities of the adjacent valve leaflets. Subsequent episodes of deposition of fibrin and recurrent organization bring about further cross-fusion of the leaflets and progressive centripetal displacement of the commissures with increasing reduction in the size of the valve aperture.

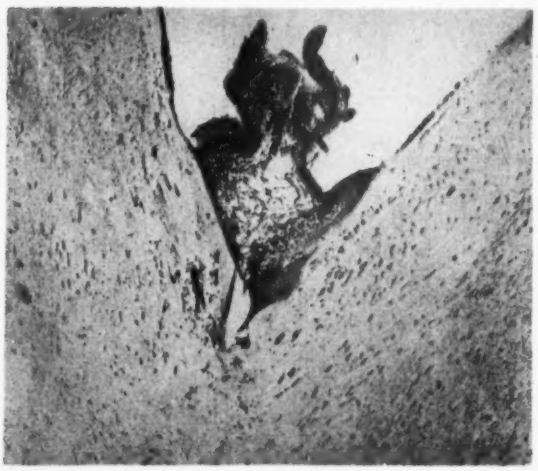


Fig. 14. Heaping up of fibrinous exudate at either valve extremity, due probably to the incessant movement of the leaflets. Organization of this mass will result in partial binding together of the adjacent leaflets. Thus the "commissures" become anatomical realities. (Magarey, F. R.: Pathogenesis of mitral stenosis. *Brit. Med. J.* 1: 856, April, 1951. Courtesy of Brit. Med. J.)

Once the opening has become sufficiently reduced, the velocity of blood flow causes sufficient trauma to induce circumferential fibrosis and further progressive narrowing of the orifice with consequent additional increase in blood velocity.[1,34] Thus, a vicious mechanism is set up which can lead only to further stenosing and further consequent physiologic deterioration. Therefore, if one is to bring about prolonged relief from mitral stenosis, it is essential that the surgically accomplished opening of the valve be appreciably larger than this critical level.

Fig. 15. A. Photograph of twigs of a tree which is coated with soft snow. Note "filleting-in" with snow of all the angles which are formed by adjacent branches.

Fig. 15. B. Authors' conception of the condition of the surface of the mitral valve during acute rheumatic valvulitis, fibrinous exudate "filleting-in" all angles formed between contiguous portions of the valve mechanism—cusps, chordae, and papillary muscle.

Fig. 16. A. Agglutination of contiguous chordae by exudate which when organized converts them into thicker rope-like structures. (Magarey, F. R.: *Brit. Med. J.* 1: 856, 1951. Courtesy of the Brit. Med. J.).

Fig. 16. B. Incorporation of the longer chordae (of the second order) within the thickened substance of the adjacent valve leaflet due to organization of enveloping exudate. (Magarey, F. R.: *Brit. Med. J.* 1: 856, 1951. Courtesy of the Brit. Med. J.).

Subvalvular Changes

Following up the analogy between the deposition of a layer of fibrinous exudate upon the valve structures and the coating of the branches of a tree by accumulation of snow or ice, one may appreciate that in many cases the exudate smoothly covers the chordae tendineae and tends to bridge or "fillet" in the angles formed between adjacent chordae, and between the leaflet and the chordae of the second order (Fig. 15 A,B).

Individual chordae become larger in caliber and less flexible due to the addition of this new fibrous tissue. Chordae attaching even to opposite leaflets may become agglutinated or

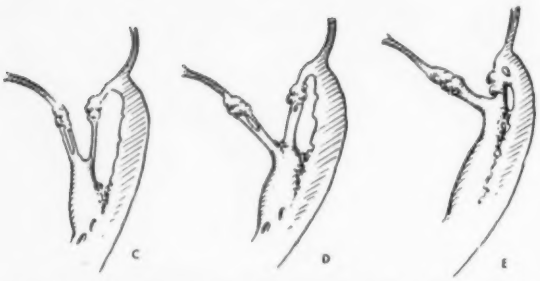


Fig. 16. C. Equal involvement of both mitral leaflets by the rheumatic process. Exudate has accumulated within the angle formed by the lateral aspect of the base of the papillary muscle and the inner aspect of the ventricular wall. D. Further progression of the process may include clumping together of the adjacent chordae and progressive fusion of the papillary muscle with the wall of the ventricle. E. The end stage may present retraction of the shrunken wall and total lateral adherence of the papillary muscle against the ventricle. The chordae supporting the septal leaflet run across the orifice of the valve.

clumped together by the enveloping exudate (Fig. 16 A). The visibly evident chordae become fewer in number and appear as thick ropelike cords rather than as thin thread-like structures. Frequently, they show new sites of apparent branching, especially as they join the valve substance. These "branchings" merely are the points at which the fusion of contiguous chordae comes to an end. In some cases, one or both of the papillary muscles may become completely or incompletely adherent laterally to the adjacent anterior or posterior left ventricular wall so that the chordae then approach the valve leaflets at an oblique angle rather than directly from below (Fig. 16, B,C,D,E).

Brock[25] has shown that exudate extending as a multiple fillet from the margin of a valve cusp over the web of adjacent chordae of the first order may, by organization, result both in "lengthening" of the cusp and a direct attachment of the papillary muscle to the apex of the abnormal valve leaflet (Fig. 17 A,B,C).

It can be readily understood how such cross-fusion and absorption of the chordopapillary supports may result in the anchoring together of the leaflets so that unless this secondary or subvalvular stenosis is separated at the time of intrinsic leaflet mobilization, any initial relief necessarily will be of limited degree, and recurrence of the obstruction within a relatively short time may be predicted with certainty.[35] After all, the pathologic condition will have come to simulate that of a fibrous stricture (See Fig. 1 A,B). and the great propensity of such strictures to recur after simple surgical division is well known.

Calcification

Calcification develops within the involved areas in many cases (38 per cent). This calcification may be considered from the surgeon's standpoint to assume one of three forms. A portion of one or both leaflets or a commissure may become stiffened and infiltrated generally

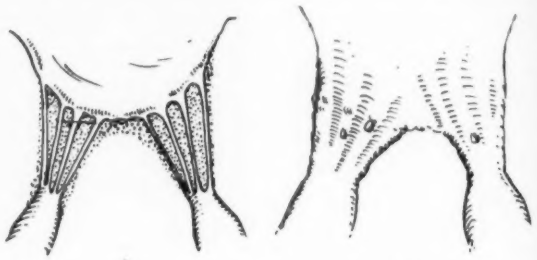


Fig. 17. A. Multiple "filleting-in" with exudate of the angles formed by the web of attaching chordae and the valve margin. B. Organization of this exudate results in "lengthening" of the valve at the expense of a portion of the length of the chordae.

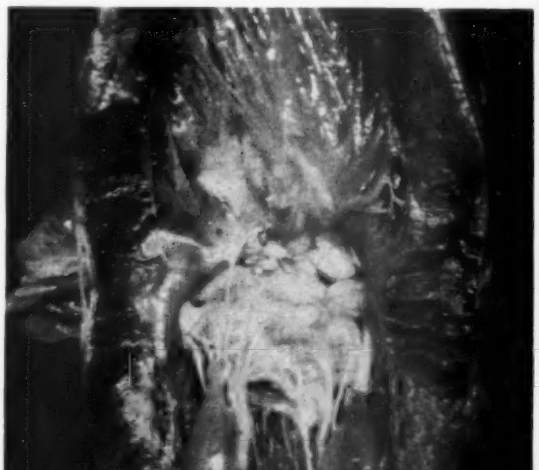


Fig. 17. C. Actual photograph of a mitral valve (from the aspect of the outflow tract) in which such "lengthening" of the septal cusp has taken place.

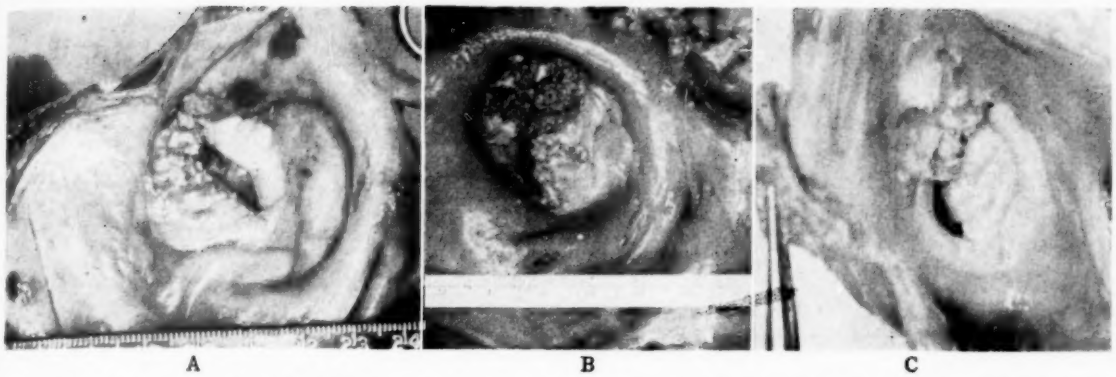


Fig. 18. Calcification of the mitral valve (atrial aspect). A. Subtotal infiltration of a valve leaflet with relatively little distortion of the surface except at one extremity of the valve. B. Sand-like surface encrustation of the edges and surface of the mitral valve (plus some deeper involvement). There is great risk, when opening such a valve, of dislodging a calcific fragment and thus causing arterial embolization. C. Block-like calcification of one extremity of the mitral valve (and the septal leaflet). The orientation of the commissure may be uncertain and proper surgical mobilization may be extremely difficult with such a valve.

with calcific salts, the overlying endothelial surface remaining relatively intact, and the outlines of the valve orifice appearing relatively normal (Fig. 18 A).

The second variety of calcific deposition is a "sand-like" or "barnacle-like" type of surface encrustation (Fig. 18 B) which does not preclude ready mobilization of the valve components, but implies great risk of arterial embolization due to the ease of dislodgment of loosely attached calcific particles during the required valvular manipulations.

In the third type, the calcific involvement is concentrated into one or more elevated block-like masses (Fig. 18 C) which may severely distort the valve orifice, or strategically occupy a commissure. While embolization may be produced by instrumental "chipping off" of a fragment from such a calcific mass, the chief difficulty in attempts to separate such valves lies in the technical problems concerned with orientation within the distorted anatomy of the structure, and in the mechanical obstacles to commissural separation which such a mass may present. Such a massive block also may involve the annulus and thus limit the possibility of full functional restoration.

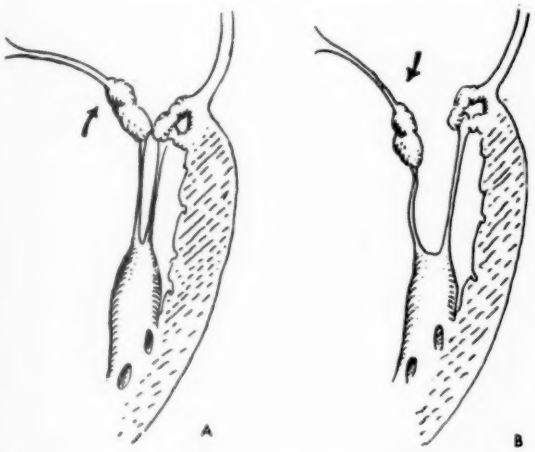


Fig. 19. Even though the involvement of the two major leaflets may be equal in extent, the greater length of the septal cusp from free margin to base permits it to function by "bending" upon its uninvolved flexible basal portion though the mural leaflet be totally rigid (See Fig. 13). A. Equally involved rheumatic mitral cusps during systole. B. During diastole the (mobilized) septal leaflet, hinged upon its mid-portion, floats away from its shelf-like mural fellow.

Clinical Basis of Neo-strophingic Mobilization

In 1954, after nearly six years of experience with the clinical application of the original concept of simple linear enlargement of the valve slit in more than 2,000 patients with disease of the mitral valve, it became evident to the senior author (CPB) that there was much to be desired in the operative procedure as then practiced. In cases with advanced pathology, it often was found impossible to secure a significant degree of functional restoration of the valve. Not infrequently a significant element

of regurgitation inadvertently became imposed upon the stenotic valve during efforts to enlarge its orifice, especially when an attempt was made to open the posteromedial commissure by instrumental means. When a reinforcing secondary subvalvular stenosis was found to exist, it was not always possible to separate it; extreme surgical efforts in this direction occasionally were attended by the creation of severe valvular insufficiency due to loss of chordal support. A small but apparently irreducible incidence of arterial embolization occurring at the time of surgery added significantly to the operative mortality and morbidity.[12,36–38]

It was appreciated that many of these difficulties were based upon the technical disadvantages inherent in any approach to the mitral valve by way of the left auricular appendage (which necessitates manipulation with an awkwardly bent finger or an extremely angulated instrument). Meanwhile, our attention had been directed toward the right side of the heart as a route of approach by some early unusual types of cases[10] and subsequent efforts led to the development of a very efficient approach to the mitral valve by way of the interatrial groove (on the right side of the heart). A detailed exposition of the technical advantages and the clinical superiority of this method of attack has been presented elsewhere.[11,12] The most important surgical advantage is related to the facility with which a nearly straight finger or instrument can be brought into line with the left atrioventricular channel, and likewise into alignment with the papillary muscles. Thus, effective manipulation or instrumentation is feasible at both valve commissures, and *either* papillary muscle may be split longitudinally with relative ease should this be found to be advisable.

An additional great advantage is related to obviation of the necessity for traversing the frequently thrombosed left auricular appendage. However, while this technical advance enabled us routinely to perform a superior type of valve mobilization, bicommissural separation being accomplished in over 95 per cent of all operative cases (nearly 500 to date), the procedure remained essentially but an improved version of the operation designated variously as "commissurotomy," "valvulotomy," "valvuloplasty," or "valvotomy."

It was not until September 26, 1955, that one of us (CPB) deliberately accomplished a complete mobilization of the greater mitral leaflet in a very severely deformed valve. The technic has been described as "rehinging of the septal leaflet" or "neo-strophingic mobilization of the septal leaflet."[39] The latter leaflet is a relatively long one, measuring (as Chiechi has shown) from 1.9 cm to 3.2 cm from its base on the annulus fibrosus to the central portion of its free margin. Even when extreme thickening, fibrosis, or calcification has rendered rigid and distal that marginal third of its substance, its middle third often, and its basal third nearly always, will be found to be thin, flexible, and grossly free of disease.

It readily can be realized that an equal extent of involvement of the shorter mural cusp in many cases must render the latter totally rigid, since it averages only 1.2 to 1.4 cm at its deepest.[17] Thereafter, it can contribute in no way to valve function except to act as an arcuate shelf protruding into the atrioventricular canal against which a mobile septal leaflet might abut (Fig. 19 A,B).

If one is able to free the septal leaflet anatomically at either extremity to a point somewhat beyond the limits of gross pathologic change, the leaflet will be enabled to "bend" upon its flexible proximal and middle thirds, and, hence, to move freely in response to the normal hydrodynamic impulses which effectuate the movement of the mitral valve. However, since the thickened and retracted mural leaflet and the junctional tissues usually will have been rendered immobile by the disease, the valve action then will become essentially that of a great unicuspid flap valve (Fig. 20 A,B,C) similar to that of the turtle valve (See Fig. 10 A,B,C).

Of course, free mobility of the septal leaflet cannot be established if any significant degree of unrelieved chordopapillary cross-fusion is permitted to exist. This is especially true in those advanced cases in which the papillary muscles have become adherent directly to the apex of the valve; it also is true to a lesser extent in those cases in which the harness of chordal suspension has become shortened.

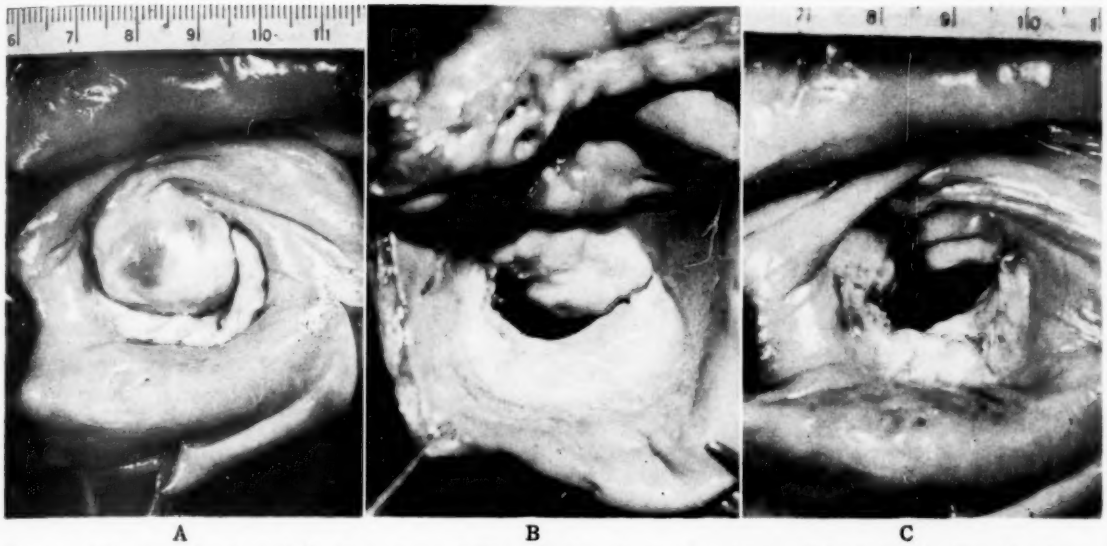


Fig. 20. Neostrophingic mobilization of a calcific stenotic mitral valve accomplished during life (death was caused by cerebral embolization). Compare with the unicuspid valve of the turtle, shown in Fig. 10 A, B, C. A. Mobilized valve in closed position (patient supine). B. Valve partially opened. Note that the rigid mural leaflet does not move. Note also the irregular margin from which a calcific fragment became dislodged during surgery. C. Valve open showing the great restoration of function which is entirely dependent upon the "hinging" of the mobilized septal leaflet upon its flexible mid-portion.

Fortunately, it has been found possible routinely to split or divide the papillary muscles in the line of their fibers in such a way that the respective valve leaflets thereafter become individually suspended. Complete digital separation of these muscles to their ventricular attachments (Fig. 21 A,B,C,D) so that each becomes converted into two structures, does not appear to diminish valve competence. One may say that the fully mobilized septal leaflet becomes hinged then upon its own independent and freely mobile chordopapillary system as well as upon its flexible middle or basal third.

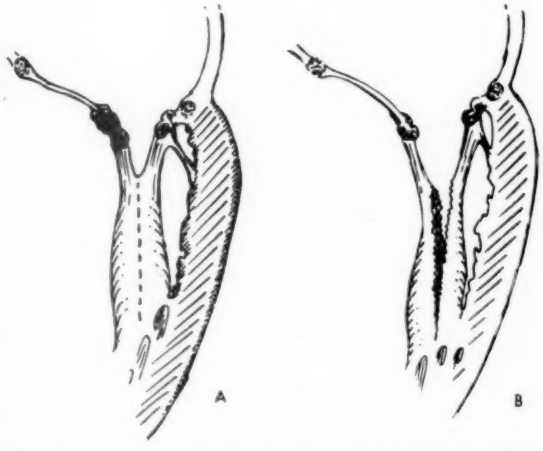


Fig. 21. A. Even though the septal leaflet be fully mobilized from the remainder of the valve "ribbon," its diastolic divergence necessarily will be restricted if the major cusps are bound together at the valve poles by either a directly adherent chordopapillary fusion mass, or a shortened chordal yoke. B. In such cases, the authors deem it essential to split the involved papillary muscle to its base. Usually this may be accomplished by end-on digital pressure alone. Rarely, instrumentation may be required.

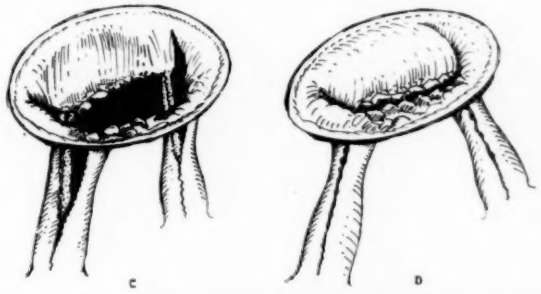


Fig. 21. C. Full neostrophingic mobilization of the septal leaflet involving separation both of the valve ribbon and of the papillary supports. Valve open. All valvular function is due to the movement of the septal leaflet. D. Valve closed, showing that competence is not compromised by this anatomic type of mobilization.

Surgical Accomplishment

While our problem has been complicated by the frequent coexistence of additional valvular disease,[40,41] (Table II), an attempt has been made to correlate the operative mortality, morbidity, and clinical course with the technical and functional achievement of each surgical procedure for mitral stenosis in Tables III, IV, and V. In Group 1 (Table III), the valve opening was considered to have been restored by neo-strophingic mobilization to a normal or larger than normal size, and the function of the fairly flexible valve was estimated to be 100 per cent of normal. Insufficiency, if present, was considered to be insignificant at the conclusion of the operation. In Group 2, the anatomic opening was judged to be close to 100 per cent of normal, but due to immobility of the fibrosed or calcified mural leaflet or inability completely to mobilize one of the valve extremities, the final functional result was considered to be about 90 per cent. Regurgitation, if present, was considered to be less than 1 plus in severity. In Group 3, the result was considered to be acceptable although one or both extremities of the semicircular line of valve closure remained incompletely opened. In some instances, this was due actually to inability mechanically to complete the separation of the valve or the subvalvular structures. More often, the effort at mobilization was terminated because of the appearance of a small regurgitant jet at the apex of the surgical cleavage. In these patients, the anatomic opening varied from 80 to 100 per cent of normal, but limitations in valvular mobility and/or the presence of a regurgitant jet restricted the functional capacity of the valve perhaps to as little as 50 per cent of normal. These procedures were considered to be the clinical equivalent of the former operation of mitral "commissurotomy," well performed from the *right* side. As such, they were technically superior to the usual commissurotomy performed from the left. Group 4 cases were those in which a significant element of unrelieved chordopapillary cross-fusion or extreme pathologic change at one or both poles of the valve restricted free leaflet mobility. In five instances it was deemed impossible physically to separate the subvalvular structures with the instruments then available. Group 5 cases were those in which regurgitation was created or increased to a serious level. In six of these 19 patients a moderate (2 plus) grade of mitral insufficiency existed prior to surgery.

TABLE II

Incidence of Multivalvular Involvement in the Cases in Which the Mitral Septal Leaflet was Rehinged (282 Cases)

	Number of cases	%
Aortic valvular involvement	22	7.8
Minor changes 7		
Required definitive surgery 15		
Tricuspid valvular involvement recognized*	55	19.5
Minor changes 41		
Required commissurotomy 14		

* 237 tricuspid valves were explored.

From this it will be seen that a completely satisfactory neo-strophingic mobilization was accomplished in 70 per cent of our series. More recent experience suggests that we now can maintain a significantly better "batting" average than this. However, in an additional 10 to 20 per cent of the original series, the technical achievement was considered to be equal or to be superior to that which would have been achieved by the older commissurotomy technic. In most cases, the failure to achieve full mobilization was due to a decision to compromise once a minimal regurgitant jet became apparent at once or both commissures.

Summary of Our Experience with Rehinging of the Septal Leaflet

This surgical technic has been attempted in 282 patients with mitral stenosis up to January 1, 1957. Thus, a follow-up of 12 to 29 months is provided. The overall pattern of valvular involvement in these patients is presented in Table II. Because of the coexistence of aortic valvular disease, a severe grade of tricuspid valve pathology, serious mitral regurgitation,

TABLE III

Estimates of Accomplishment in Restoration of the Mitral Valve Both Anatomically and Functionally

Group		Number of cases	%
I	Valve function 100% (anatomic opening 100%) 50		
II	More than 80% of valve function restored 106	156	69
III	More than 50% of valve function restored	23	10
IV	Limited valvular opening	29	13
	Due to extreme pathologic change 24 (11%)		
	Subvalvular fusion incompletely relieved 5 (2%)		
V	Created or increased regurgitation	19	8
Total		227	

or a significant element of incompleteness of the hospital records, 55 cases were deleted from this study. Thus, we have 227 patients in whom an effort was made to rehinge the septal leaflet for essentially "pure" mitral stenosis or isolated mitral stenosis with clinically insignificant mitral regurgitation.

Mobilization of the Septal Leaflet: Many surgeons, including the authors, have attempted to express the size of the stenotic or opened mitral valve in such terms as "finger-tip," "one finger," "one and one-half fingers," "two fingers," etc. Others have estimated the length and breadth of the orifice in millimeters or centimeters. Neither method is entirely acceptable anatomically; first, because it is nearly impossible to evaluate the size of the orifice accurately by either criteria, and, second, because of physiologic variations in the size of the aperture and of the annulus fibrosus in health (because of the range of the patient's size) and in disease (large left ventricle, small left ventricle). Furthermore, such linear and cross-sectional designations, even if they were accurate, could scarcely express the degree of function or of valvular adequacy. In this article, we have attempted to correlate the anatomic and functional result in terms of the *per cent of normal* with due consideration of the normal size of the annular ring in each particular individual (Table III and Table VI). It will be noted that in 21 cases, or more than 30 per cent of the 71 patients with an incomplete valvular mobilization, the aperture was considered to be of "two finger" size.

Some bilateral separation of the commissures was obtained in all but nine cases of this series (4 per cent). However, full commissural mobilization was not obtained in 52 patients (23 per cent) (Table III).

Subvalvular Stenosis: In this series, the stenotic mitral valves of 99 patients were considered to be free of significant cross-fusion of the subvalvular structures. The remaining 128 were recognized to have some element of subvalvular or secondary stenosis (Table VII A). In at least 24, both poles of the stenotic valve were thus reinforced. Chordopapillary fusion limited to the posterior pole of the valve was three times as common as that localized anteriorly (76 : 28). Direct papillary fusion to the valve apex was

TABLE IV

Operative Mortality of Operations for Mitral Stenosis

	Number of Cases	Operative deaths
Mitral commissurotomy from the left side (before Jan. 1955)	1,000	77 (7.7%)
Mitral commissurotomy from the right side (before Sept. 1955)	150	13 (8.6%)
Neostrophingic mobilization (from Sept. 1955 to Jan. 1957)	227	11 (4.8%)
Compromised technical result (less than 80% valvular function restored)	71	7 (10%)
Good technical result (more than 80% valvular function restored)	156	4 (2.5%)

TABLE V

Results of Follow-Up Studies on 159 Patients Operated on for Mitral Stenosis by Rehinging the Septal Leaflet Compared with the Results in 792 Patients Having a Mitral "Commissurotomy" by the Left Thoracic Approach

	Excellent	Improved	Total improved	Same	Worse	Total follow-up cases
From the right side (12 to 27 months postoperatively)						
Ideal or nearly ideal functional valvular opening obtained	65	45	110 (96%)	5 (4%)	0	115
Less satisfactory valvular opening established	21	22	43 (98%)	1 (2%)	0	44
From the left side (1 to 7 years postoperatively)						
All patients	—	—	711 (89.8%)	49 (6.2%)	32 (4%)	792

TABLE VI

Relationship of the Estimate of Percentage of Function to the Opening Measured in "Fingers" in Cases of Neostrophingic Mobilization

	More than 90% functional opening	Less than 90% functional opening	Total number of cases
More than 2 fingers	16 (80%)	4 (20%)	20
2 fingers	86 (80%)	21 (20%)	107
1¾ fingers	47 (62%)	29 (38%)	76
1½ fingers or less	7 (2.9%)	17 (71%)	24
Total	156	71	227

TABLE VII(A)

Chordopapillary Involvement

		Number of cases	%
No subvalvular involvement recognized		99	43.6
Subvalvular involvement		128	56.4
Anterior subvalvular changes		28	
Papillary fusion to valve	8		
Chordal agglutination	20		
Posterior subvalvular changes		76	
Papillary fusion to valve	46		
Chordal agglutination	30		
Bipolar subvalvular changes		24	
Papillary fusion to valve	16		
Chordal agglutination	8		
Total		227	100

recognized in 70 patients, while chordal cross-fusion alone was present in 58. In 32 instances, no definitive treatment was considered necessary (Table VII B). In 84, direct end-on pressure with the finger tip (perhaps aided by "knife-like" action of the operator's fingernail) sufficed to separate the subvalvular chordal fusion or to split extensively a directly

TABLE VII(B)

The Results of Treatment of Subvalvular Stenosis in the Cases of Mitral Reconstitution

		Number of cases
Major subvalvular stenosis		96
Complete relief	64	
Physiologically reasonable function obtained	12	
Unsatisfactory separation	20	
Minor subvalvular changes (not treated)		32
No subvalvular stenosis		99
Total		227

adherent papillary muscle. In each of the latter cases, an attempt was made to split the muscle fully to its ventricular origin, thus converting it into two individual or separate muscles. This was accomplished fully in 64 patients. In 12 patients, definitive instrumentation was required for the relief of the subvalvular obstruction.

Production of Mitral Regurgitation: Because the arcuate line of valvular closure must be extended

at both extremities into the region of flexible valve substances, it is inevitable during the course of surgery that minor grades of insufficiency (expressed as a "whiff" or a "one-plus" palpable regurgitant jet) frequently will be created or superimposed upon a pre-existing insufficiency. The first appearance of such a jet should serve to interdict any further digital or instrumental attempt at separation of the valve at that pole. Indeed, it is this necessity for recognition of the very beginning of created or aggravated valvular incompetence that renders open surgery (with hypothermia or the heart-lung apparatus) for mitral stenosis so extremely dangerous. Such beginning incompetence developing during the course of valvular mobilization can scarcely be appreciated unless the heart and valve are functioning and carrying the full load of the circulation.

While it is emphasized that the arcuate line of valve closure should be fully re-established or even exaggerated, great care must be exercised during the accomplishment, especially while making the upward turn at either extremity of the valve crescent. Both the "nether" and the "supernal" tip of the "horned moon"[12] should be re-established, but they should never approach each other. Neither should the septal leaflet be detached from the annular ring lest great regurgitation result, as shown in Figure 22. This accident can be avoided by increasing familiarity with the technic and by advancing the separation only a little at a time, always refraining from the application of great force.

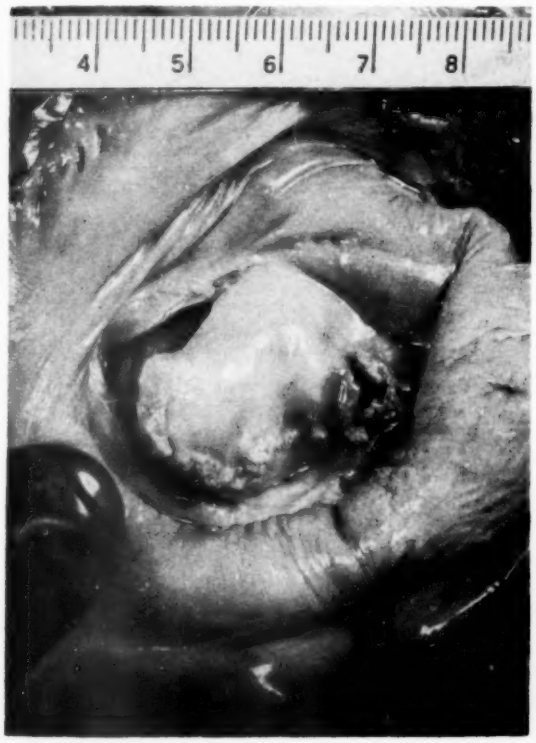


Fig. 22. Photograph showing detachment of the septal leaflet from the annulus fibrosus due to application of too great an amount of force during neostrophingic mobilization of the valve. Death resulted from massive regurgitation.

The implementation of the concept of rehinging of the septal leaflet necessitates the frequent production of a very minor degree of incompetence, but certainly great increments of created insufficiency should not be permitted to occur. Nevertheless, as shown in Table VIII, it did occur occasionally in this, our beginning experience with this procedure. Among the 19 patients in whom moderate to severe insufficiency existed at the conclusion of surgery, six were believed to have had equal grades of incompetence preoperatively.

TABLE VIII

Pre and Postoperative Changes in Valve Competence in 227 Cases of Mitral Reconstitution

	Preoperative grade of regurgitation	Postoperative grade of regurgitation			
		None	Minor	Moderate	Severe
None	167	51	111	3	2
Minor	54		46	7	1
Moderate	6			6	
Total	227	51	157*	16*	3*

* It may be noted that only 76 cases had a systolic murmur postoperatively.

Calcification of the Valve: In this series, 75 patients (33 per cent) had minimal to maximal grades of calcification of the leaflets or junctional tissues, or both (Table IX). The anatomic

TABLE IX

Incidence of Calcification of the Valve in 227 Cases of Mitral Reconstitution

	Number of cases	%
Calcified valve	75	33
Minimal degree 41		
Moderate degree 23		
Heavily calcified 11		
No calcification	152	67
Total	227	100

and functional results obtained in these technically more difficult problems were nearly as good as those achieved in the noncalcified valve (Table X). These results are in dramatic

TABLE X

Influence of Calcification of the Mitral Valve Upon Final Functional Valvular Opening

	More than 80% functional opening obtained	Less than 80% functional opening obtained	Total
Fibrotic non-calcified valve	110 (71.7%)	42 (28.3%)	152
Partially or heavily calcified valve	46 (61.4%)	29 (38.6%)	75
Total	156	71	227

contrast with the characteristically much poorer technical accomplishments which all cardiac surgeons have experienced when operating upon the calcified valve by way of the left-sided approach. Gratifyingly, there appeared to be no greater likelihood of production of incompetence during reconstitution of the calcified valve.

Atrial Thrombosis: One of the great mechanical advantages of the right-sided approach to the mitral valve is that it does not require manipulation or transgression of the frequently thrombosed left auricular appendage. When the left-sided approach is employed, gross evidence of fresh or organized clotting within the appendage is found in over 50 per cent of the patients with atrial fibrillation.[1] These, in turn, make up about one-half of all of our operative patients. Hence, the left auricular appendage will be found to be thrombosed in over one-quarter of the individuals who seek surgical help for mitral stenosis. Since such clots, inadvertently fragmented or dislodged during intracardiac surgical manipulations, are believed to be the usual cause of operative embolization, it would seem to follow logically that this complication should be relatively less common with the right-sided approach to the mitral valve.

In this series (Table XI), true intra-atrial thrombosis was recognized in 23 instances, the

TABLE XI

Recognized Incidence of Thrombosis of the Left Atrium

		Number of cases
Thrombus		23 (10%)
Loose fresh thrombus	18	
Required removal	5	
Not disturbed	13	
Placenta-like organized thrombus (not disturbed)	5	
No thrombus felt		204
Total		227

clot usually protruding in cauliflower fashion from the auricular appendage, but sometimes attached to the lateral or posterior atrial wall and lining it like a placenta. In 18 instances, the thrombus was felt to be a relatively newly-formed, non-organized mass. In five cases, one-third or more of the left atrial chamber was occupied by a huge clotted mass. In another five instances, the clot was found freely floating or so loosely attached that its dislodgment was considered imminent. In each, the semisolid mass was morcellated and aspirated successfully by insertion of the appropriate sized Litwak suction tip into the atrium along the palmar surface of the operator's left index finger (Fig. 23).

Arterial Embolization: Arterial embolization

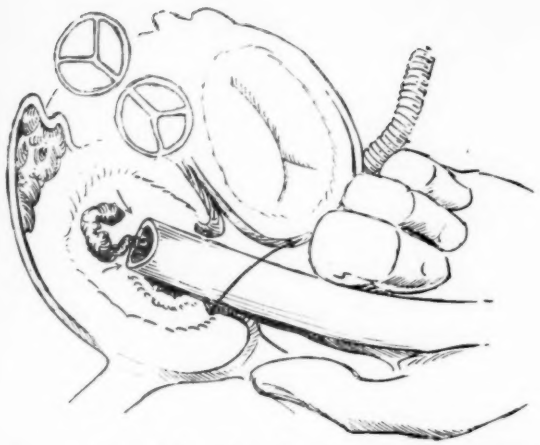


Fig. 23. Use of the Litwak aspirator tip to remove freely floating or loosely attached thrombi from the left atrium. The tip is passed along the operating finger into the heart, and is applied against the surface of the clot. Then the suction motor is turned on. Large clots become morcellated during extraction. Since a large amount of blood is aspirated during this procedure, it is necessary slightly to overtransfuse the patient before carrying it out.

complicated the operative intervention in 7 patients (3 per cent as compared to 7 per cent by the left-sided approach).[1] This was cerebrovascular in five, peripheral in two (Table XII). It was believed in each instance that these embolic issues were due to inadvertent dislodgment of calcific particles from the valve edge rather than fragments of an intra-atrial thrombus. In comparison with the older operative procedure (left-sided commissurotomy) embolization was significantly less common.

TABLE XII

Incidence and Mortality of Arterial Embolization in 227 Cases of Mitral Reconstitution Operated from the Right Side Compared with that in 811 Cases Operated from the Left Side*

	Mitral reconstitution (neostrophingic mobilization)		Mitral "commissurotomy" (operated from the left side)	
	Non-fatal	Fatal	Non-fatal	Fatal
Cerebral	3	2	14	16
Extremity	2		7	3
Pulmonary			2	6
Visceral			3	1
Cerebral plus one of above			1	2
Total	5 (2.2%)	2 (0.9%)	27 (3.3%)	28 (3.5%)
Total (all types)	7 (3.1%)		55 (6.8%)	

* As previously reported (Baily, C. F.: *Surgery of the Heart*, Lea and Febiger, Philadelphia, 1955, p. 544).

Operative Mortality: There were 11 operative deaths in this series (Table XIII). In retrospect, it is felt that at least three of them (cases of acute pulmonary edema) were due to the inclusion of extremely ill patients (Type IV) in this series. The deaths attributed to the creation of serious mitral insufficiency and to hemorrhage are considered to have been the result of technical errors on the surgeon's part. In a previous study,[11,12] it was shown that the operative mortality in patients with left-sided or right-sided mitral "commissurotomy" procedures varies by less than 1 per cent. It will be noted that the operative mortality (Table IV) was significantly lower with neo-strophingic mobilization than with either of the older less complete procedures, and that it was further lowered (2.5 per cent) whenever the mobilization was especially good.

TABLE XIII

Cause of Death in 227 Cases of Mitral Reconstitution

	Number of cases	Mortality
Ideal or nearly ideal operative accomplishment	156	4
Cerebral embolism 1		
Hemorrhage 1		
Acute pulmonary edema 2		
Less satisfactory opening of valve	71	7
Cerebral embolism 1		
Hemorrhage 1		
Acute pulmonary edema 2		
Created or increased mitral regurgitation 3		
Total	227	11 (4.8%)

Febrile Complications: The so-called "post-commissurotomy syndrome" or a prolonged, poorly explained febrile reaction (which might be so described) was observed in 11 patients, or 5.1 per cent (Table XIV). The low incidence

of this complication was attributed, in part, to assiduous lavage of the pericardial sac with saline solution prior to closure.

Abolition of Murmur: The diastolic murmur and the sharp first sound at the apex were abolished to auscultation and to phonocardiographic recording in nearly one-half of the entire series (Table XV, A,B) (Fig. 24 A,B). Perhaps the

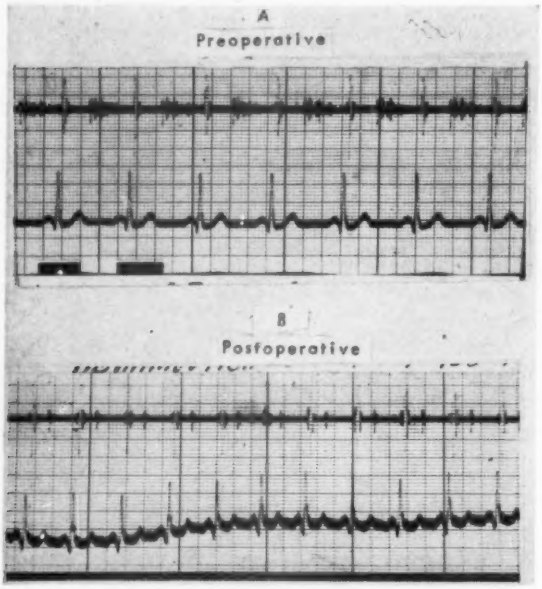


Fig. 24. Phonocardiograms showing abolition of the diastolic murmur in a patient with mitral stenosis. A. Preoperative tracing. B. Phonocardiogram obtained three months after a satisfactory neostrophingic mobilization of the mitral valve.

residual roughening and stiffening of the leaflets may be responsible for maintaining these abnormal sounds in some cases even after full neo-strophingic mobilization.

A systolic murmur was produced in 34 per cent. This could not be correlated with the production of insufficiency during surgery. In some cases, it was associated with tricuspid incompetence.

TABLE XIV

Postoperative Febrile Reaction in 227 Cases Following Mitral Reconstitution

	Number of cases	Febrile reaction	%
Ideal or nearly ideal cases	156	6	4
Less satisfactory cases	71	5	7
Total	227	11	5

TABLE XV(A)

Postoperative Disappearance of Mitral Diastolic Murmur after Neostrophingic Mobilization (Phonocardiographic Determination)

	Number of cases	Disappearance of diastolic murmur
Complete or nearly complete restoration of valvular function	148	75 (52%)
Incomplete restoration of valvular function	56	25 (34%)
Total	204	100 (49%)

TABLE XV(B)

Postoperative Disappearance of the Sharp First Mitral Sound After Neostrophingic Mobilization (Auscultatory Determination)

	Number of cases	Disappearance of sharp first mitral sound
Complete or nearly complete restoration of valvular function	119	55 (46%)
Incomplete restoration of valvular function	44	23 (50%)
Total	163	78 (42%)

Postoperative Condition: The follow-up has been from 1 year to 27 months (Table V). The clinical condition of the patients by all objective measurements appears to be significantly better than that previously obtained with the older operation.

Conclusions

After nine years of experience with the standard left-sided operation for mitral stenosis, the authors have become impressed with its several significant shortcomings and disadvantages. The chief and most serious of these drawbacks are:

(1) The very limited mobilization of the valve which routinely is achieved (20 to 50 per cent of normal).

(2) The increasing evidence that there is a high incidence of recurrence of mitral obstruction after the passage of several years.

(3) A seemingly irreducible incidence of production of significant regurgitation.

(4) An unsatisfactory clinical course in a fair number of patients, probably caused for the most part by a combination of the first three disadvantages.

(5) A certain irreducible incidence of arterial embolization due to the necessity for insertion of the operating finger into the heart by way of the frequently (25 per cent) thrombosed left auricular appendage.

(6) An overall operative mortality of approximately 8 per cent.

Feeling that a more satisfactory mechanical mobilization offered the best chance of overcoming these discouraging features, a concerted attempt was made to improve the surgical aspects of the operation. The bare-finger technic, the right-sided approach to the valve, the perfection of certain instrumental adjuvants, and finally a *complete alteration in surgical concept* were successively adopted.

In brief, the pathologic deformation of the mural leaflet and the junctional tissues usually is so complete that any hope of restoring the normal bicuspid flutter-valve mechanism of mitral leaflet action is unrealistic. On the other hand, the fibrosis and distortion of the substance of the longer septal leaflet, while equal in actual measurement of involvement to that of the mural, is limited to the distal or marginal third of its apicobasal length. Hence, the middle and basal thirds of this cusp remain thin and flexible, and readily capable of acting as a hinge if the leaflet mobilization is extended at each extremity well beyond the area of scarring. (Fig. 20 A,B).

The frequent association of directly adherent papillary muscles, or shortening of the chordae represents another source of restriction of valve mobility. However, by definitively splitting these muscles longitudinally to their ventricular origin, the septal leaflet also may become "hinged" upon them as well as upon its own flexible basal substance.

Thus an irretrievably destroyed flutter-valve may be converted into an efficient flap-valve by a feasible surgical technic which has been described under the term "Neo-strophingic mobilization of the septal leaflet."

Now that our experience with this procedure has encompassed more than 200 cases, we feel justified in stating that the routinely accomplished restoration of valve function is far superior to that obtainable with any other existing technic. The incidence of embolization and created regurgitation has been low even in this beginning series. In half of all patients, the diastolic murmur of mitral stenosis has been completely abolished by the operation. The operative mortality has been much lower than that established over the years with the older left-sided approach. The morbidity has been strikingly less.

It is felt that recurrence of mitral obstruction following the older type operation is inevitable in many patients since that procedure consists essentially of dividing a fibrous stricture. On the other hand, since neo-strophingic mobilization involves the creation of an entirely new type of valve, and since all of the definitive surgical separations extend into the zone of thin, flexible tissue well beyond the area of pathological change, it is believed that recurrence of mitral obstruction following this operation will be rare indeed.

The manifest superiority of neo-strophingic mobilization of the septal leaflet by the right-sided approach over the older type of surgery has been demonstrated. It is the feeling of the authors that, as the members of the medical profession become more familiar with these advantages, this procedure inevitably must supersede and replace the former operation.

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Experimental Studies

Metabolic Studies on the Arrested and Fibrillating Perfused Heart*

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THE OXYGEN consumption and substrate utilization of the beating heart have been the subject of a large series of publications.[1] Observations on the oxygen usage of the arrested and fibrillating heart are less numerous and data on substrate utilization of the arrested and fibrillating heart are not available.[2,3] The introduction of surgery on the arrested human heart has made these studies of practical importance.[4] In addition, an estimation of the oxygen consumption of the arrested heart is essential in re-evaluating previous figures on myocardial efficiency.[1] In previous calculations of myocardial efficiency, values for the oxygen consumption of the beating heart were used without making allowance for the "basal" myocardial oxygen consumption.[5] If the oxygen usage of the arrested heart represents an appreciable fraction of that of the beating organ, previous estimates of myocardial efficiency are too low. To study these problems, information must be obtained on the perfused arrested and fibrillating heart. This has been accomplished by Lorber and by Gregg.[2,3] The former found that the oxygen usage of the fibrillating heart exceeds that of the rhythmically contracting organ.[2] Maintaining extremely low perfusion rates, he estimated the oxygen consumption of the fibrillating heart to be about 40 per cent above that of the normally beating heart. Gregg and his co-workers found that the oxygen usage of the arrested heart amounted to about 16 to 40 per cent of the working heart with normal sinus rhythm.[3] There was a rapid decline of the myocardial oxygen usage immediately following induced asystole. It is the purpose of this paper to describe results on myocardial extraction and usage of oxygen, glucose, pyruvate, lactate and ketones obtained on the physiologically perfused heart in situ performing its usual external work, on the artificially perfused empty heart beating with normal sinus rhythm, and on the arrested and fibrillating organ. Comparative studies were performed in open and closed chest anesthetized dogs.

MATERIAL AND METHODS

The experiments were performed on a total of 40 mongrel dogs anesthetized with intravenous sodium pentobarbital (30 mg/kg weight). Heparin (50 mg) was injected intravenously to prevent clotting. Two series of experiments were performed. In the first, the technic of Gregg was followed.[6,7] The chest of the animal was opened and artificial respiration was begun. With the dog in the left lateral position, a brass cannula was introduced from the left brachiocephalic artery through the aorta into the left coronary artery. Previously, a polyethylene tube had been inserted into the coronary sinus through the right atrial appendage. Artificial respiration was then stopped and the left coronary artery was perfused by gravity from a reservoir placed at a height of two meters. The blood was oxygenated, maintained at a temperature of 38° C, and slowly stirred by an automatic device. Coronary inflow was not measured, but the rate of outflow from the coronary sinus was determined either directly by collection in a graduate

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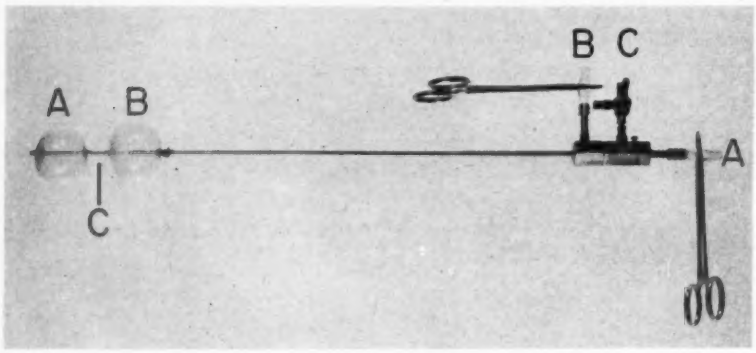

Fig. 1. The triple lumen catheter used in the perfusion of the coronary arteries of dogs with closed chest. The catheter is introduced through the carotid artery into the left ventricle and the aorta. Balloon A lies in the outflow tract of the left ventricle. It prevents flow of perfusate through the incompetent aortic valve. The balloon A communicates with opening A at the top of the catheter. Balloon B is situated in the proximal aorta just distal to the sinus of Valsalva. It prevents flow of perfusate into the distal aorta. The balloon communicates with opening B. C represents the openings through which perfusate leaves the catheter to enter the sinus of Valsalva and the coronary artery. Stopcock C communicates with these openings.

cylinder or by a recording rotameter.[7] Samples of blood entering the coronary artery were drawn from the tubing connecting the reservoir with the arterial cannula. Coronary sinus blood was collected from the polyethylene catheter. Potassium chloride (500 mg) was then injected into the coronary artery to arrest the heart.[4] It was also added to the perfusion reservoir making a total concentration in the perfusate of 0.5 per cent.

This procedure is time-consuming. The chest has to be opened, and handling of the heart often induces fibrillation before control observations can be made. Therefore, another technic was devised which eliminated opening of the chest and intubation of the coronary artery. After insertion of a catheter into the coronary sinus under fluoroscopic control, a catheter was placed into a femoral artery.[8] The coronary blood flow was then measured with the nitrous oxide method and samples of blood were drawn from the coronary sinus and the femoral artery for determinations of substrates.[5] A special triple lumen catheter was then inserted into the left internal carotid artery and the tip of this catheter was advanced to the aortic valve. The purpose of this catheter is to perfuse all the coronary arteries of the animal through the sinus of Valsalva. Thus, escape of the blood into the aorta and the left ventricle must be prevented. This is accomplished by the two balloons, illustrated in Fig. 1. A metal lumen catheter is then introduced into the right atrium through an external jugular vein. Cardiac rhythm is monitored through an electrocardiogram. The triple lumen catheter is then advanced through the aortic valve into the left ventricle.

The balloon, placed in the left ventricular outflow tract, is inflated with 40 cc of air. Immediately afterwards, the aortic balloon is also inflated and perfusion of the coronary arteries is begun. Blood flow is usually kept at approximately 40 cc/min with a Sigma motor. The volume of inflow is graphically recorded with a recording rotameter.[7] Simultaneously, with perfusion of the coronary artery, blood is suctioned through the metal catheter from the right atrium to keep the cardiac chambers bloodless.

Usually, the empty heart continues to beat with normal sinus rhythm for several minutes. Blood samples are collected from the coronary sinus and the arterial inflow for analysis of oxygen and substrates. From 500 to 800 mg of potassium chloride are then injected into the coronary artery through the catheter, and potassium chloride is also added to the perfusion reservoir making a total concentration of 0.5 per cent in the perfusion reservoir. This usually induces several minutes of ventricular fibrillation during which further samples are obtained. After cardiac arrest, perfusion is continued for periods ranging from 5 to 40 minutes, and samples are withdrawn at intervals ranging from 1 to 10 minutes. Following termination of each experiment, concentrated Evans blue dye is injected into the tube leading to the sinus of Valsalva. The chest is then opened, the position of the balloons is verified, and the blue discoloration of the myocardium is used as evidence that the coronary arteries had been adequately perfused.

Blood for analysis of oxygen and nitrous oxide was collected in lightly oiled syringes to which eight drops of heparin had been added. Samples were analyzed for oxygen and nitrous oxide on the manometric apparatus of Van Slyke and Neill.[9,10] For the collection of substrates, blood was collected in dry syringes and immediately transferred to 20 cc bottles containing crystalline

TABLE I

Open Chest Perfusion—Mean Values

Dog	A-CS O_2 Δ (ml/100 ml)			O_2 Δ Usage (cc/min)			Lactate A-CS Δ (mg/100 ml)			Glucose A-CS Δ (mg/100 ml)			Ketone A-CS Δ (mg/100 ml)			Pyruvate A-CS Δ (mg/100 ml)		
	Controls	F	A	Controls	F	A	Controls	F	A	Controls	F	A	Controls	F	A	Controls	F	A
1	12.20	—	5.60	1.20	—	0.30	7.8	—	2.8	—	—	—	—	—	—	0.070	—	−0.260
2	20.30	—	14.69	6.30	—	1.78	—	—	—	−18.2	—	2.3	—	—	—	—	—	—
3	16.83	12.04	13.97	10.10	7.21	8.38	− 6.1	− 1.2	—	−42.2	−14.4	—	—	—	—	−1.280	−0.806	—
4	14.50	—	4.25	2.90	—	2.83	− 2.5	—	− 1.4	9.0	—	5.3	—	—	—	−1.260	—	−0.106
5	—	7.09	5.64	—	2.12	0.87	—	− 2.8	− 7.6	—	9.4	4.5	—	—	—	—	−1.142	−0.672
6	16.25	—	9.25	3.25	—	0.35	12.6	—	7.7	−23.1	—	12.0	—	—	—	−0.085	—	−0.110
7	12.38	—	4.36	1.58	—	0.74	2.4	—	− 0.5	− 0.7	—	− 2.6	0.04	—	−0.09	−0.801	—	−0.285
8	7.47	8.08	6.49	1.01	1.66	0.75	− 0.6	2.2	− 0.1	− 1.2	− 2.9	3.1	0.08	0.06	0.30	−0.672	−0.826	−0.624
9	—	4.65	3.66	—	1.22	0.43	—	− 5.6	5.0	—	5.6	3.6	—	0.25	−0.13	—	−1.188	−0.406
10	7.84	—	6.98	2.74	—	0.44	− 1.9	—	−13.4	5.6	—	6.7	0.51	—	−0.08	−0.214	—	−0.223
11	16.99	—	12.10	5.47	—	1.93	−13.1	—	− 9.2	17.0	—	6.6	0.34	—	−0.08	0.029	—	0.067
12	—	14.12	9.03	—	5.83	1.44	—	− 2.1	− 5.3	—	14.0	13.5	—	0.34	0.09	—	0.082	−0.118
13	11.90	—	8.50	1.37	—	1.12	2.5	−10.4	− 2.0	1.3	—	2.3	0.03	—	−0.19	−0.100	—	−0.253
14	—	7.87	16.87	—	2.61	2.66	—	—	—	—	—	—	—	—	—	—	−0.970	0.034
15	5.45	—	4.92	1.01	—	0.57	2.0	—	0	9.3	—	5.0	—	—	—	−0.412	—	−0.336
16	5.20	—	6.48	1.06	—	0.64	− 1.8	—	− 6.6	8.5	—	11.2	0.19	—	0	−0.190	—	−0.577
17	—	4.30	4.07	—	0.94	0.97	—	−28.3	−12.8	—	—	—	—	−0.19	−0.44	—	−0.228	−0.400
18	—	3.60	4.80	—	3.67	1.29	—	−12.4	−14.3	—	3.6	9.0	—	0.46	0	—	−1.059	−0.942
19	—	3.00	3.02	—	1.80	0.75	—	− 3.8	− 2.2	—	3.2	5.2	—	−0.33	1.12	—	−0.405	−0.901

A = Arrest.
F = Fibrillation.

TABLE II

Open Chest Perfusion—Mean and Significance of the Difference

	Oxygen usage (cc/min)					Glucose, mean A-CS Δ (mg/100 ml)					Pyruvate, mean A-CS Δ (mg/100 ml)				
	Mean	SE	Range of mean	P	N	Mean	SE	Range of mean	P	N	Mean	SE	Range of mean	P	N
C	5.56					−21.7					−0.976				
F	4.44					− 8.2					−0.816				
C-F	1.12	1.77	−0.65 to 2.89	>.6	2	−13.5	14.7	−27.8 to 1.7	>.5	2	−0.160	0.314	−0.474 to 0.154	0.7	2
C	3.17					0.75					−0.364				
A	1.65					5.19					−0.272				
C-A	1.52	0.38	0.07 to 4.52	<.01	12	− 4.56	4.25	−35.1 to 10.4	>.3	10	−0.092	0.095	−1.154 to 0.387	>.3	10
F	3.01					5.5					−0.717				
A	1.95					6.6					−0.415				
F-A	1.06	0.53	−4.39 to 1.17	>.05	9	− 1.1	1.75	− 4.9 to 6.0	>.5	6	−0.302	0.151	−0.200 to 1.004	>.05	8
	Oxygen content, mean A-CS Δ)ml/100 ml)					Lactate, mean A-CS Δ (mg/100 ml)					Ketones, mean A-CS Δ (mg/100 ml)				
	Mean	SE	Range of mean	P	N	Mean	SE	Range of mean	P	N	Mean	SE	Range of mean	P	N
C	12.15					− 3.3									
F	10.06					0.5									
C-F	2.09	2.75	0.62 to 4.79	>.5	2	− 3.8	1.05	− 4.9 to 2.8	>.1	2					
C	12.28					0.7					0.20				
A	8.13					− 2.3					−0.02				
C-A	4.15	1.01	−1.28 to 10.25	<.01	12	3.0	1.35	− 3.9 to 11.5	>.05	10	0.22	0.11	−0.22 to 0.59	>.1	6
F	7.19					− 7.9					0.10				
A	7.51					− 8.3					0.16				
F-A	−0.32	1.27	−5.09 to 9.00	>.8	9	0.4	3.64	−18.6 to 15.5	>.9	8	−0.06	0.30	−0.46 to 1.45	>.8	6

A = Arrest.
C = Control.
F = Fibrillation.

TABLE III

Closed Chest Perfusion—Mean and Significance of the Differences

	Oxygen usage (cc/min)					Glucose, mean A-CS Δ (mg/100 ml)					Pyruvate, mean A-CS Δ (mg/100 ml)				
	Mean	SE	Range of mean	P	N	Mean	SE	Range of mean	P	N	Mean	SE	Range of mean	P	N
C	24.88					2.13					0.175				
NSR	5.37					− 1.31					0.054				
C-NSR	19.51	1.87	11.94 to 29.14	<.001	9	3.44	12.97	−32.7 to 83.6	.8	8	0.228	0.305	−0.603 to 1.797	>.4	7
C	24.92					3.23					0.010				
F	5.33					0.40					0.313				
C-F	19.59	3.60	9.67 to 43.96	<.001	9	2.83	14.35	−34.6 to 78.7	>.8	7	0.302	0.156	−0.171 to 0.891	0.1	7
C	25.11					4.05					0.123				
A	4.83					− 0.21					0.384				
C-A	20.28	2.26	4.74 to 43.17	<.001	17	4.26	9.13	−50.2 to 60.6	>.6	17	0.506	0.155	−0.348 to 2.322	>.001	16
NSR	6.63					13.48					0.110				
F	5.72					17.25					0.213				
NSR-F	0.91	1.18	−1.60 to 5.41	>.9	5	3.78	8.18	−22.8 to 13.2	>.6	4	0.103	0.063	−0.050 to 0.247	0.3	4
NSR	5.72					− 1.31					0.054				
A	4.54					16.80					0.449				
NSR-A	1.18	0.68	−2.10 to 4.28	>.1	8	−18.11	5.31	−38.4 to 6.3	>.01	8	0.395	0.114	−0.038 to 0.940	>.01	7
F	5.33					0.40					0.313				
A	4.88					1.10					0.400				
F-A	0.45	0.59	2.10 to 3.25	.4	9	0.70	9.37	−21.1 to 43.2	>.9	7	0.088	0.067	−0.116 to 0.397	>.2	7

	Oxygen content, mean A-CS Δ (ml/100 ml)					Lactate, mean A-CS Δ (mg/100 ml)					Ketones, mean A-CS Δ (mg/100 ml)				
	Mean	SE	Range of mean	P	N	Mean	SE	Range of mean	P	N	Mean	SE	Range of mean	P	N
C	15.43					6.59					1.01				
NSR	11.84					2.01					0.15				
C-NSR	3.59	1.63	−4.00 to 10.44	>.05	9	4.57	6.89	−22.2 to 20.8	>.5	7	0.86	0.46	−0.64 to 2.39	>.1	7
C	14.87					8.07					0.67				
F	10.36					− 9.90					0.65				
C-F	4.52	1.71	−4.10 to 11.15	>.02	9	17.97	2.52	7.1 to 25.1	<.001	7	1.31	0.312	0.06 to 2.51	>.001	7
C	14.77					6.64					0.61				
A	8.35					− 9.37					0.56				
C-A	6.42	1.27	−3.43 to 13.90	<.001	17	16.00	3.90	15.2 to 48.5	<.001	16	1.17	0.470	−2.95 o 5.03	>.02	15
NSR	12.05					− 8.55					0.13				
F	10.30					−12.40					0.37				
NSR-F	1.75	2.21	−2.75 to 10.27	>.9	5	3.85	1.29	0.4 to 6.6	>.05	4	0.24	0.49	−1.14 to 1.09	>.6	4
NSR	11.76					2.01					0.15				
A	8.58					−12.86					0.82				
NSR-A	3.18	1.28	0.23 to 9.34	>.02	8	14.87	4.43	− 3.0 to 29.1	>.01	7	0.97	0.47	0.04 to 3.61	>.05	7
F	10.36					− 9.90					0.65				
A	8.45					−15.97					1.50				
F-A	1.91	1.16	−0.93 to 7.99	>.1	9	6.06	3.27	− 3.4 to 23.4	>.1	7	0.85	0.35	−0.15 to 2.52	>.05	7

A = Arrest. C = Control. F = Fibrillation. NSR = Normal Sinus Rhythm.

TABLE IV

Closed Chest Perfusion—Mean Values

Dog	Oxygen usage (cc/min)				Glucose A-CS Δ (mg/100 ml)				Pyruvate A-CS Δ (mg/100 ml)			
	Control	NSR	F	A	Control	NSR	F	A	Control	NSR	F	A
1	20.70	—	3.98	0.73	− 0.5	—	−79.2	−61.1	−0.153	—	−0.019	−0.083
2	17.50	—	6.93	6.81	15.6	−68.0	—	−39.4	−0.310	0.293	—	0.018
3	15.10	2.65	—	2.56	14.1	—	—	− 4.2	0.036	—	—	−0.141
4	22.10	—	—	1.74	5.5	—	—	−71.2	0.339	—	—	0.147
5	34.20	—	—	4.87	16.5	—	13.2	− 8.7	−0.141	—	−0.291	−0.300
6	22.50	5.84	5.30	5.54	2.4	—	—	− 5.9	0.294	—	—	−0.557
7	47.60	—	3.66	4.43	8.2	6.8	− 6.4	11.9	−0.350	−0.528	−0.478	−0.490
8	19.50	7.56	9.16	6.44	0	11.8	34.6	50.2	0.628	−0.002	−0.249	−0.489
9	29.10	7.43	2.02	3.15	0.9	29.0	—	22.7	1.055	−0.742	—	−1.267
10	34.20	5.06	—	2.08	0	—	—	22.8	0	—	—	−0.747
11	25.30	—	—	3.33	− 3.7	− 5.6	—	24.2	—	—	—	—
12	20.50	2.58	—	—	1.7	−19.8	—	6.0	0.082	0.514	—	−0.426
13	30.10	4.91	—	3.13	0	—	—	12.6	0.488	—	—	−0.149
14	17.40	—	—	1.13	9.8	—	—	21.1	0.058	—	—	−0.219
15	24.10	—	—	19.36	4.1	—	− 0.2	−43.4	−0.175	—	−1.066	−0.950
16	14.50	—	4.83	3.40	− 3.3	29.4	23.5	44.6	−0.059	0.123	−0.124	−0.093
17	28.00	8.80	8.80	10.90	− 2.4	5.9	17.3	14.2	0.177	−0.034	0	−0.397
18	24.90	3.50	3.30	2.50	—	—	—	—	—	—	—	—

A = Arrest. F = Fibrillation. NSR = Normal Sinus Rhythm.

sodium fluoride. Blood glucose was determined enzymatically with the method of Teller.[11]

Pyruvate was determined according to the method of Friedemann and Haugen, using a trichloroacetic acid filtrate.[12] Lactate was measured with the method of Barker and Summerson.[13] Ketones were determined with the modification of the micromethod of Greenberg and Lester.[14] As shown in previous publications, the heart usually removes substrates from the coronary artery blood.[1] This is referred to as positive myocardial extraction, or positive myocardial balance of the respective substrate. In some instances, however, the concentration of a substrate in coronary venous blood may exceed that in arterial blood. This is then referred to as negative myocardial balance or negative myocardial extraction of the respective substrate.

For comparative and statistical purposes, all values for myocardial usages obtained on the closed chest animal were expressed for the whole heart. Since, with the triple lumen catheters all coronary arteries were perfused, the product of coronary arteriovenous difference times the coronary inflow represented the usage of substrate of the whole heart. However, as the nitrous oxide method measures blood flow through 100 g of myocardium only, myocardial usages thus obtained per 100 g had to be converted for the whole heart by multiplying them by the weight of the heart.[5] The latter was obtained from the total weight of the animal by the formulae of Herrmann[15] and Smith.[16]

For the statistical work-up of the data, paired algebraic differences were recorded for each animal and in each classification for which usable data were available. In each case the "student" t test was applied to test the null hypothesis that the mean difference was zero.

The probability value "p" was obtained from tables printed elsewhere.[17, 18]

Results

Results on the Open Chest Animal: Data obtained on the open chest animal are summarized in Tables I and II. It may be seen from Table II that there was a fall in myocardial oxygen usage from the control period (heart beating with normal sinus rhythm) to fibrillation, from control period to cardiac arrest, and from ventricular fibrillation to cardiac arrest. The decline in oxygen usage from the control period to cardiac arrest was statistically significant, while that from fibrillating to the arrested heart was of borderline significance (Table II). The myocardial oxygen extraction fell likewise from control to fibrillation and from control to arrest; the latter result was statistically significant.

No significant changes in the myocardial extraction of glucose, pyruvate, lactate and ketones occurred in these animals during ventricular fibrillation or cardiac arrest (Table II). Severe injury to the heart muscle was indicated by the findings that in five animals during the control period, the myocardial glucose balance was negative (Table I). For example, in one animal, the glucose concentration in the coronary sinus blood exceeded that in the arte-

TABLE IV—Continued

Closed Chest Perfusion—Mean Values

Oxygen A-CS Δ (ml/100 ml)				Lactate A-CS Δ (mg/100 ml)				Ketones A-CS Δ (mg/100 ml)			
Control	NSR	F	A	Control	NSR	F	A	Control	NSR	F	A
15.22	—	9.96	1.97	3.9	—	−20.0	−23.2	−0.09	—	−1.90	−2.31
15.41	—	17.19	17.00	− 2.7	19.5	—	12.5	0.60	0.68	—	−0.15
14.15	6.64	—	6.41	4.2	—	—	0.2	0.23	—	—	−0.87
14.78	—	—	5.26	8.3	—	—	20.3	—	—	—	—
13.56	—	—	14.20	8.6	—	1.5	− 4.5	1.05	—	−0.67	−0.53
20.34	9.90	9.15	9.56	10.8	—	—	−14.0	−0.53	—	—	2.42
17.12	—	6.67	7.06	12.2	− 4.5	−11.1	−20.9	1.72	−0.67	0.47	−0.78
16.95	12.53	15.28	7.62	10.0	− 2.2	− 6.3	− 8.6	1.28	−0.14	−1.23	−3.75
10.11	13.54	3.27	4.20	10.2	6.6	—	−13.9	2.77	0.69	—	0.03
19.00	12.67	—	5.20	3.8	—	—	− 8.4	1.02	—	—	−0.72
13.20	—	—	8.55	—	—	—	—	—	—	—	—
17.52	12.51	—	—	2.9	22.2	—	− 6.9	−0.05	0.18	—	0.14
15.10	14.47	—	12.50	12.6	—	—	− 7.9	0.40	—	—	0.23
15.00	—	—	2.80	− 0.4	—	—	−20.0	−0.04	—	—	0.95
12.40	—	—	10.95	8.3	—	− 1.2	− 2.4	0	—	−0.49	−1.87
13.00	—	7.90	5.52	3.6	−17.2	−21.5	−44.9	0	0.64	−0.06	−0.59
12.70	16.70	16.80	16.13	9.9	−10.3	−10.7	− 7.3	0.72	−0.34	−0.64	−0.64
13.02	7.60	7.00	7.00	—	—	—	—	—	—	—	—

rial perfusate by 42 mg/100 ml of glucose (Experiment No. 3, Table I). In the other ten animals in which observations during both the control period and arrest were available, the mean myocardial glucose extraction was very low, due to the fact that in four of these animals the myocardial glucose extraction was negative (Table II). Similar results were obtained with lactate and pyruvate (Table II). In the group in which observations were available during the control period and during cardiac arrest, five out of ten animals had a negative myocardial lactate extraction during the control period (Table I). In one control experiment (No. 11), the lactate concentration in coronary sinus blood exceeded that in arterial blood by 13.1 mg/100 ml (Table I). Negative myocardial balances of lactate were also obtained during cardiac arrest and ventricular fibrillation, but the changes were not statistically significant (Table II).

Table I illustrates that myocardial pyruvate balances were negative in the majority of animals during the control period, during cardiac arrest, and during fibrillation. The myocardial extraction of ketones was less affected (Table I). All myocardial extractions of ketones during the control period were positive. Some negative balances were recorded during myocardial arrest and fibrillation.

Results on the Closed Chest Animal: Values obtained in the closed chest animal show a significant fall in myocardial oxygen usage from the naturally perfused heart on one hand, to the artificially perfused empty heart or the arrested and fibrillating heart on the other (Table III). Apparently, the oxygen usage of the beating heart was primarily determined by its external work. No statistically significant change in myocardial oxygen usage existed between the artificially perfused empty heart and the fibrillating and arrested heart (Table III). In four out of nine experiments, the myocardial oxygen usage of the arrested heart even exceeded that of the fibrillating organ (Table IV). This finding is in contrast to that of Lorber, who found in the heart-lung preparation a significantly greater myocardial oxygen usage during fibrillation than during rhythmical contraction.[2] Since the coronary flow was predetermined and did not alter greatly during the experiment, the changes in myocardial oxygen usage reflected alterations in myocardial oxygen extraction.

Data on myocardial extraction of glucose, pyruvate, lactate and ketones are summarized

in Tables III and IV. In contrast to control data accumulated on the open chest animal, the myocardial balances of substrates were positive in the majority of experiments (Table IV). With the exception of pyruvate, in which one control group only showed a slightly negative myocardial balance, mean values for myocardial extractions were positive (Table III). In three out of eight experiments in which the empty heart was beating without performing any external work, the mean myocardial glucose balance became markedly negative (−5.6, −19.8, and −68.0 mg/100 ml) (Table IV). In some instances, the mean myocardial glucose balances were also negative during ventricular fibrillation (three animals) and cardiac arrest (seven animals) (Table IV). In one of these experiments, the concentration of glucose in the coronary sinus exceeded that in arterial blood by more than 103 mg/100 ml. The relationship of these values to the glucose concentration in the perfusate will be discussed later.

Negative myocardial lactate balances were also observed in four out of seven experiments in which the empty heart was beating with normal sinus rhythm, (range of from −2.2 to −17.2 mg/100 ml) (Table IV). However, negative myocardial lactate balances were much more frequent during ventricular fibrillation and cardiac arrest (Table IV). As a result, the mean values for arteriovenous lactate differences became markedly negative and were statistically significant from the controls ($p < 0.01$, Table III). This illustrates that marked glycolysis takes place in the arrested and fibrillating perfused heart despite a sufficient amount of oxygen transported to the heart muscle.

The incidence of negative myocardial pyruvate balances was even greater than in the case of glucose or lactate (Table IV). Even during the control period, the myocardial balances of pyruvate were negative in 6 out of 16 experiments (Table IV). In the empty perfused heart with normal sinus rhythm, the mean myocardial pyruvate balances were negative in four out of seven experiments (Table IV). Negative pyruvate balances were observed in five out of seven hearts with ventricular fibrillation and in 14 out of 16 hearts with complete arrest (Table IV). Similar negative myocardial pyruvate balances had been previously found in hemorrhagic shock and in artificial myocardial infarction.[19,20]

Results obtained on the myocardial extraction of ketone bodies are illustrated in Tables III and IV. It may be seen that the incidence of negative myocardial balances of ketones increased greatly during ventricular fibrillation and cardiac standstill.

Discussion

This report deals with comparative values on the metabolism of the naturally perfused heart in situ, the empty artificially perfused rhythmically contracting heart in situ, and the fibrillating and arrested perfused heart. The first series of experiments were carried out on the open chest animal, using cannulation of the coronary sinus and the left coronary artery. The rate of flow from the coronary sinus was measured. According to Gregg, about 64 to 83 per cent of the blood from the left coronary artery drains through the coronary sinus.[21,22] Although the relationship of coronary sinus flow to coronary artery flow may vary in different experiments, changes in coronary sinus flow serve as a directional indicator of left coronary inflow. There is a significant decline in the oxygen usage from the normally contracting heart to the arrested organ (Table II). The myocardial oxygen usage of the arrested heart is slightly less than that of the fibrillating organ, but this difference is not statistically significant (Table II). In many instances, the myocardial extraction of substrates is negative, not only during arrest and fibrillation, but already during the control period in which the perfused heart was rhythmically contracting in the open chest animal (Table I). It is probable that the severity of the myocardial disturbances which are encountered are the result of difficult experimental conditions. The time elapsed between opening of the chest and onset of perfusion of the left coronary artery is considerable. This, together with the actual trauma to the heart muscle during the procedure may be responsible for some of the results obtained.

Data obtained with the closed chest animal using the triple balloon catheter are of greater

physiologic validity. In these experiments, all coronary arteries are perfused, coronary inflow rather than outflow is measured, and the time between control and experimental observation is short, since opening of the chest and cannulation of the coronary arteries are not necessary. One of the sources of error in this procedure is the possibility of leakage of the perfusion fluid into the left ventricle around the balloon placed into the left ventricular outflow tract. In early tests, this possibility was considered when dye, injected into the sinus of Valsalva through the catheter, appeared in the left ventricular cavity within a few seconds. However, the same phenomenon is observed in experiments in which the left circumflex coronary artery is intubated and the dye is injected into this vessel through the catheter. This suggests that channels connecting the coronary circulation with the ventricular chambers may be of greater importance in the arrested than in the rhythmically contracting heart. Further studies have confirmed the absence of leakage around the ventricular balloon.

Using the closed chest animal, no statistical difference is found in the oxygen usage of the empty rhythmically contracting heart and the fibrillating or arrested organ (Table III). The oxygen usage in these preparations varies between 20 to 30 per cent of that of the naturally perfused heart in situ. It appears that the oxygen usage of the heart is primarily determined by its external work. In contrast to control data on the open chest animal, mean myocardial balances of glucose, lactate and ketone bodies are positive during the period when the rhythmically contracting heart is perfused (Table III). This illustrates that the damage to the heart muscle in the closed chest animal is less severe than in the open chest dog. However, metabolic disturbances are encountered in the perfused, fibrillating and arrested organ (Table III). In some instances, the glucose concentration in coronary vein blood exceeds that in the arterial perfusate by more than 70 mg/100 ml (Table IV). It has been previously found that in the normal human and dog heart, the myocardial uptake of glucose is a function of its arterial concentration.[1] This is again confirmed in the naturally perfused hearts of this series. (Slope of the regression line for control samples $b = 0.206$; $p < 0.05$ and > 0.02). For the artifically perfused hearts, however, the p value was < 0.2 and > 0.1, although the slope was approximately the same ($b = 0.236$). This illustrates that although in the artificially perfused heart the arterial glucose concentration may play a role in the determination of myocardial glucose uptake, this appears not to be the only factor.

The observation that the oxygen usage of the empty rhythmically contracting as well as the fibrillating and arrested heart is relatively high (about 20 to 30 per cent of the naturally perfused heart *in situ*), necessitates a re-evaluation of calculations of myocardial efficiency. This fact has already repeatedly been stressed by Gregg.[23] It appears likely that myocardial efficiency is considerably greater than had been previously assumed.[1]

Summary

Results are described dealing with comparative values on the metabolism of the naturally perfused heart, the empty artificially perfused beating heart *in situ*, and the fibrillating and arrested perfused heart. The studies were performed on open and closed chest dogs. Perfusion of the arrested heart in the closed chest animals was accomplished with a new technic employing a specially devised arterial catheter. This permitted perfusion of all coronary arteries and did not necessitate cannulation of the coronary arteries.

In the open chest animal, there was a significant decline in the oxygen usage from the rhythmically contracting to the arrested heart. The myocardial oxygen usage of the arrested heart was only slightly less than that of the fibrillating organ.

Myocardial extractions of substrates were mostly negative during the control period. This was probably the results of difficulties in experimental technic.

In the closed chest animal, no statistical difference existed between the oxygen usage of the empty rhythmically contracting heart and the fibrillating or arrested organ. The oxygen usage in these preparations was between 20 to 30 per cent of that of the naturally perfused heart in situ.

Mean myocardial balances of glucose, lactate and ketones were positive during artificial perfusion of the rhythmically contracting heart. These values became negative during cardiac standstill or ventricular fibrillation.

The results indicate that the oxygen usage of the heart is primarily determined by its external work; they also suggest that previous values calculated for the mechanical efficiency of the beating heart are too low.

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Review

Neurohormonal Atherogenesis*

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THE PRESENT day preoccupation of nearly all atherosclerosis investigators with lipid metabolism and dietary lipids resembles the mass-psychologic outburst of what one might call "nephromania" among hypertension researchers in the late thirties and early forties. At that time the existence of neurogenic and hormonal pathogenic mechanisms was not only totally ignored but even the mere mention of such factors was actually frowned upon as nonconforming deviationism.

The writer of the following review has certainly no reason to criticize the current wave of "lipomania," since 25 years ago he himself had devoted considerable effort to the collection of epidemiologic data from all over the world concerning the suspected role of dietary fat and cholesterol in atherogenesis.[58] Although statistically inadequate, the incoming information from hospitals, clinicians, pathologists, insurance agencies, medical missions, etc., provided, nevertheless, the strong impression that dietary fat and cholesterol do enhance atherogenesis. In 1932, a plan for internationally organized and rigidly standardized world-wide epidemiologic atherosclerosis research was submitted to the Josiah Macy, Jr., Foundation, however without arousing any particular interest at that time. Since then, encouraged by other reports,[43,81,84] similar appeals for international statistical research concerning atherogenesis and diet have been made by the writer in several publications[59,61,66,68,69] until at long last the systematic large-scale organization of this type of work by Ancel Keys[35] and its endorsement by Paul D. White produced convincing results, especially concerning coronary atherosclerosis. The significance of these extensive investigations is being widely recognized. Only a few investigators and the dairy industry regard them with skepticism.[11]

Gofman's[23] studies of qualitative cholesterol metabolism and serum lipoproteins, recent emphasis on the atherogenic differences between saturated and unsaturated fats in the diet, and innumerable related observations have contributed a great deal of useful knowledge. However, they have at the same time almost drowned out any interest in the fundamental question as to whether excessive fat and lipid intake and alterations of cholesterol metabolism are really the alleged all-dominating primary features of atherogenesis, or whether other factors, primarily predisposing the vascular walls for the acceptance and deposition of lipids, may not be of equal, or even greater importance.

Friedman *et al.*[22] have questioned the supreme initiating role of cholesterol in atherogenesis and have instead placed emphasis on observations which suggest that a fibroblastic proliferation of the intima as a predisposing condition often precedes any detectable lipid deposition in coronary artery branches.

In the following discussion, certain angiotoxic

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factors, such as infections, extrinsic chemicals, etc. will not be included. Attention will be called instead to the potentially pathogenic role of the neurohormone-discharging vegetative nervous system, particularly regarding epinephrine and norepinephrine, and the modification of their atherogenic effectiveness by other hormones.

EXPERIMENTAL ANGIOTOXIC AND ATHEROGENIC EFFECTS OF EPINEPHRINE AND NOREPINEPHRINE. LIPID LINKAGES

Necrotizing and subsequently calcifying lesions of the medial layers of the large arteries (resembling Moenckeberg's sclerosis) as a result of the experimental injection of large doses of epinephrine have been known for a long time.[32] However, they are of lesser interest for the problem of intimal atherogenesis than the development of a thickening of the intima in both large and small vessels of rabbits and dogs after the prolonged administration of small doses of epinephrine.[4,19,42,54] Recently, proliferations of the intima were observed by Friedman *et al.*[21] and by Masson[47] after injections of epinephrine and, to a lesser extent, of norepinephrine. Waters[90] describes epinephrine-induced elevations of the endothelium with accumulation of polymorphonuclear leukocytes and lymphocytes in the space beneath. These lesions could be prevented by the adrenolytic drug Dibenamine® and left scars after their regression.

Despite the fact that the visible structural effects of the adrenosympathogenic catecholamines on the arterial intima are less impressive than those on the media, they appear significant enough to justify the assumption that epinephrine-induced medial and intimal lesions are causally related somehow,[53,60] and that the catecholamines, by primarily injuring the intima, may prepare the ground for subsequent lipid depositions. This latter concept which had been expressed as early as 1914 by Anitschkow[1] and later by Hueck,[30] was further substantiated by Danisch[12] and by the writer[60] who observed a markedly accelerated and intensified lipid infiltration of the aortic intima in cholesterol-fed rabbits after injections of either plain epinephrine or epinephrine-containing lipid extracts from the adrenal glands and from human serum.

Recent investigations of Dury *et al.*[15–17] suggest that epinephrine also influences lipid metabolism itself in that it increases the neutral fat, phospholipid, and cholesterol content of the serum, augments the incorporation of phosphorus and promotes the formation of phospholipids in the aortic wall of the rabbit. The specific affinity of epinephrine and norepinephrine to lecithin with which they form compounds soluble in organic solvents,[34,52,64] the apparent synthesis of epinephrine-lipid compounds in the adrenal medulla,[40] and the exceptional ease with which lecithin penetrates into vascular tissue,[56] are probably features involved in the effects of epinephrine on lipid partition and deposition.

Electrical stimulation of the arterial walls was found to produce necrotizing lesions of the media[42] analogous to those elicited by epinephrine. Since these experiments undoubtedly affected also the supplying sympathetic fibers, the electrical stimulation of which is accompanied by a local discharge of norepinephrine,[70] it appears probable that the vascular lesions observed were actually due to the latter factor.

Coronary atherosclerosis in cholesterol-fed animals was reported as being greatly accentuated by enforced excessive exercise on the treadmill,[75] which is another sympathetic stimulating and catecholamine-discharging procedure.[62] Nicotine provokes catecholamine discharges from both the adrenal medulla and the sympathetic ganglia.[67,71] Its administration was likewise found to elicit necrotic lesions of the arterial media[76] and to aggravate the development of cholesterol atheromatosis.[12]

VASCULAR LESIONS IN CASES OF PHEOCHROMOCYTOMA AND IN RENAL EXCRETORY INSUFFICIENCY

Once epinephrine and norepinephrine are recognized as experimentally atherogenic agents, it stands to reason that they may also be considered from the point of view of their potential role in spontaneous clinical atherogenesis.

In this connection, the vascular status of pheochromocytoma patients is of interest, although the majority of these tumors discharge

mostly norepinephrine, the metabolic and angiotoxic properties of which are not quite as pronounced as those of epinephrine.[25] Unfortunately, no systematic statistics are available but generalized arteriosclerosis and atheromatosis, occasionally also necrotizing arteriolitis, have been observed as common findings in untreated adult cases.[32] Even more significant is the recorded presence of such vascular lesions in young children.[8,38,92] Coronary sclerosis has been observed in pheochromocytoma patients as young as ten years.[8] The easily detectable involvement of the retinal vessels[7,27,29] may reach excessive degrees and has been seen to disappear completely after surgical removal of the catecholamine-discharging tumor.[10]

Severe arterial hypertension, in the pathogenesis of which the neurogenic sympathetic factor usually plays a significant part,[66] seems to be paralleled, even though not regularly, by a high degree of coexisting atherosclerotic vascular lesions.[9]

Russian workers[80,89] have observed an aggravation of experimental cholesterol atheromatosis through simultaneous production of renal hypertension. The well-known phenomenon of nephrogenic arterial necrosis, although differing in acuity and distribution from the slowly developing atherosclerosis of the large arteries, may nevertheless represent a basically related process of more rapid vascular degeneration. Its dependence on severe renal excretory insufficiency,[24] and its aggravation by a high-fat diet[28] have been attributed to the hypothetic toxic action of hypothetic "metabolites," accumulated in the blood.[31] Intimal lipid depositions are also intensified by renal excretory insufficiency.[88] Since advanced renal failure in humans is regularly accompanied by a marked elevation of the blood catecholamine level, as observed by the writer[65,73] and as later confirmed by others,[18,46] this factor may be assumed to constitute a significant contributory element in the vascular lesions of patients with kidney pathology.

INDIRECT CATECHOLAMINE EFFECTS INDUCED BY OTHER HORMONES (THYROXIN, INSULIN)

The findings of Lehr *et al.*[44] that parathyroidectomy and thyroidectomy prevent the arterial necroses which otherwise result from artificially induced renal insufficiency, make it probable that other hormonal factors are also involved in the origin of those vascular lesions. As far as the thyroid hormone is concerned, its powerful potentiation of catecholamine action[5,66] is likely to represent an important connecting link. Accordingly, the epinephrine- and norepinephrine-induced sclerosis of the aortic media and proliferation of the intima are greatly intensified by thyroid hormone administration[21,74] while they can be prevented by thyroidectomy.[74] Moreover combination of epinephrine with thyroxin was found to intensify the development of cholesterol atheromatosis.[53] By itself, the thyroid hormone protects the intima from experimentally induced cholesterol infiltrations, presumably by depressing the blood cholesterol level, "but it does not seem to reduce the incidence of spontaneous atherosclerosis in the chick".[83]

No detailed reference will be made here to the rather extensive literature concerning adrenocortical effects on vascular structure (lesions by desoxycorticosterone acetate; protection against cholesterol atheromatosis and nephrogenic vascular necrosis by cortisone and hydrocortisone) since there is no reason to speculate on a direct interference of these corticoids in the angiotoxic action of the neuro-hormonal catecholamines.

The recent observations of Pick *et al.*[55] concerning the provocation of severe aortic and coronary atheromatosis by hypoglycemia-producing doses of insulin, are probably attributable to the intense discharges of epinephrine from the adrenal medulla which occur regularly during insulin hypoglycemia.[66]

HYPOXIATING-NECROTIZING ACTION OF CATECHOLAMINES

The ultimate mechanism by which the adreno-sympathogenic catecholamines exert their toxic effects on the arterial media and intima is still problematic but most observers agree on the probability of a state of local hypoxia as the decisive feature. This hypoxia has been tentatively ascribed to either a functional constrictive[42] or endothelial proliferative[54] narrowing of the vasa vasorum, or to the increased hydrostatic pressure of the blood against

the vascular walls during epinephrine action.[90] Experimental attempts to produce vascular lesions through the mechanical application of extreme intravascular pressure have given negative results however.[33]

Since the catecholamines are exquisitely calorigenic, oxygen-wasting agents,[66,67] if present in exaggerated concentrations, their direct chemically hypoxiating action on the vascular walls appears to be the most likely cause of their angiotoxic effects (in analogy to their more extensively studied and well-known hypoxiating and necrotizing action on the heart muscle.[66,67]) A similar view was expressed by Miculicich and Oester.[48]

In amplification of older observations by Tatum,[85] who found that epinephrine is brought to disappearance by contact with arterial tissue, recent experiments of the writer and W. Gigee[72] have shown that the arterial walls (like the heart muscle, and in striking contrast to other tissues[70]) first absorb and then gradually metabolize epinephrine and norepinephrine from the blood stream and from artificial perfusion fluids, in relatively large quantities. Ordinarily, the catecholamine content of arterial tissue consists almost entirely of norepinephrine[72,77] but injected excess epinephrine is accumulated in the arterial walls and its presence there must be considered from the point of view of its properties as an exquisitely tissue-necrotizing agent.[87] The same applies to norepinephrine, although it is not quite as readily absorbed[70,72] and is somewhat less oxygen-consuming than epinephrine.[25] The total catecholamine content of the aorta rises with advancing age and reaches a peak at about 60 years.[63]

The thyroid hormone, whose calorigenic action is mediated by the catecholamines,[5] intensifies arterial oxygen consumption.[6,36] This probably explains its aggravating effect on catecholamine-induced atherogenesis.

Some possibly pertinent biochemical observations concern epinephrine-induced alterations of the vascular protein composition,[78] preatheromatous changes in the hexosamine content, and an increase of hydroxyproline in the human aortic intima.[51]

DRUG INTERFERENCE WITH ANGIOTOXIC CATECHOLAMINE ACTION

The adrenolytic drug dibenamine was found to prevent the epinephrine-induced vascular lesions completely.[90] A protective effect which chlorpromazine has been reported to exert against cholesterol atheromatosis[93] may be caused by a reduction of catecholamine-discharging central nervous stimuli.

The possibility of preventing epinephrine- and thyroxin-induced vascular lesions and experimental cholesterol atheromatosis by such agents as choline,[57] ATP,[14] heparin,[14] and ascorbic acid[13] provides additional interesting clues but it would be premature to speculate on their mode of counteraction in terms of an interference with primary catecholamine activity.

NEUROVEGETATIVE IMBALANCES WHICH PROMOTE ANGIOTOXIC CATECHOLAMINE OVERACTION

Morphologic alterations in the ganglia and nerve fibers that supply the arterial walls have been described by several workers[12,79,82,86] as existing in human and experimental atherosclerosis, but their specificity and functional significance remains open to question.

Central nervous and psychogenic sympathetic stimulating factors in the pathogenesis of arteriosclerotic vascular lesions are particularly stressed by Mjasnikow[49] and the Russian school[3] which places great emphasis on the role of the cerebral centers in morbid conditions in general. Statistical data which suggest a higher incidence of arteriosclerosis in social and occupational situations involving greater mental tensions, responsibilities, anxieties, and frustrations[66] cannot be interpreted simply on the basis of psychic stimuli alone without consideration of other interfering factors, e.g., physical activity or inactivity, respectively. The latter, by permitting a deterioration of vagal cholinergic counter regulatory efficiency, seems to induce a harmful sympathetic adrenergic preponderance[67] and the corresponding vascular metabolic and structural alterations. The large statistics of Morris[50] and Luongo[45] concerning coronary morbidity and mortality among different occupational groups provide an impressive argument in favor of an anti-atherogenic efficacy of steady moderate exercise.

On the other hand, excessive overexertion may likewise upset the neurovegetative adrenergic-cholinergic balance in cardiovascular tissue metabolism by promoting a local overaction of catecholamines. This is suggested by animal experiments[75] and by observations concerning a limitation of arteriosclerotic lesions to extremities that had performed strenuous work over long periods of time.[37,39] An asymmetrical development of vascular anomalies in both radial arteries has been ascribed to right- and left-handedness respectively, and in persons who did a great deal of stair climbing a significantly higher incidence of peripheral arteriosclerosis was claimed to exist by comparison with non-stair climbers.[41]

The possible role of excessive tobacco smoking in the origin of arteriosclerosis in general and atherosclerosis in particular[2,20,26,91] is still unsettled from the purely statistical point of view but there can be little doubt that the well-known ganglionic-stimulating, catecholamine-mobilizing, and experimentally angiotoxic properties of nicotine qualify it as a further potential contributory factor among those which affect the vascular system by way of direct or indirect catecholamine overaction.

PROPHYLACTIC OUTLOOK

It is too early at this time to embark on any elaborate speculations concerning possible prophylactic measures to counteract the adrenosympathetic predisposing element in atherogenesis. Theoretically, a most important feature would seem to be the radical abolition of some of the main characteristics of our prosperity-ridden, declining Western civilization: the generally prevailing tendency toward physical laziness, its combination with frantic competitive striving after material "success," and the boredom and frustration which result from the hollowness of that very type of success, in so far as it is devoid of meaningful higher spiritual, intellectual, and esthetic values. Equally utopian would be the idea of restricting the cherished overindulgence in alimentary fats and the abuse of tobacco.

Whether conveniently applicable drugs to dampen catecholamine overactivity and/or to enhance cholinergic counterregulation can be developed, only time will tell. Presently available sympathoadrenolytic, ganglionic-blocking, centrally inhibitory and vagal-stimulating drugs are impractical as routine preventives, but they are likely to offer a working foundation for more successful attempts to promote a further overaging and overpopulation of the Western world. Whether or not these are desirable goals may be left to the sociologists and philosophers to decide.

SUMMARY

Current research trends seem to overemphasize lipid metabolism as the allegedly primary, initiating and dominating factor in atherogenesis, whereas the basic problem of intrinsic biochemical vascular lesions as a probably predisposing and/or permissive pathogenic factor is nearly completely disregarded.

Directly angiotoxic as well as atherogenesis-enhancing properties of the hypoxiating and potentially necrotizing adreno-sympathogenic catecholamines (epinephrine and norepinephrine) and their constant presence in the vascular walls have long been known. They are avidly absorbed by the arterial tissue and form compounds with phospholipids. Their hypoxiating and angiotoxic effectiveness is enhanced by the thyroid hormone. They may be regarded as the pacemakers for subsequent lipid infiltration of the arterial intima.

Excessive catecholamine action on the vascular walls can be assumed to exist (a) in cases of pheochromocytoma, (b) in renal excretory insufficiency with resulting catecholamine retention in the blood, (c) in conditions of emotional, reflectory, or pharmacodynamic (nicotine, etc.) sympathetic over-stimulation and (d) in conditions of deteriorating cholinergic counteraction which seems to result from physical inactivity.

These latter civilization-induced neurovegetative mechanisms, combined with an excessive consumption of fats and cholesterol, characterize arteriosclerosis and atherosclerosis as the number one "disease of prosperity."

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Franz Groedel Memorial Lecture

The Humanities in Medicine*

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I AM DEEPLY moved by the honor and privilege of delivering the Franz Groedel Memorial Lecture this year. I ask you to accept my sincere thanks.

It is interesting, indeed noteworthy, that the late William G. Kerckhoff, who gave Dr. Franz M. Groedel, whom this lectureship commemorates, funds to build at Bad Nauheim a laboratory to be devoted to research in cardiovascular disease, also gave the California Institute of Technology in Pasadena funds to build the William G. Kerckhoff Laboratories of the Biological Sciences, of whose staff I am a member.

Franz Groedel sought, from the beginning of his career, to use the methods and instruments of physics in medicine; he was one of the pioneers of clinical electrocardiography. The Kerckhoff Laboratories of Biology were built at Pasadena to bring to biology the methods and ideas of physics, chemistry, and mathematics.

The title of the Groedel Lecture is "The Humanities in Medicine." It is to "serve as a yearly reminder of our humanistic obligations." The hope was expressed that it may "inspire us to take an active role in shaping the motivations of the medical student and the ideals of the graduate." The title implies that there are problems such as how to bring together the humanities and medical science, how medical practice may be scientific and yet kept consonant with the patient as a person. Both kinds of problems are related. It is a matter of mixing vinegar and oil. In medicine, as a science, the proper manner is objectivity, rigor, and unexcusing logic. Eloquence, personal warmth, sympathy, and temperament are eccentricities in science; they are the life blood of the humanities.

There is a danger that we may be using the term "the humanities" as if it meant the same as "humane." My old Webster's Collegiate Dictionary defines "humane" as

> "Having feelings and inclinations creditable to man; benevolent. Synonyms: kind, merciful, compassionate, sympathetic, tenderhearted, lenient, clement, forgiving."

"The humanities" the same dictionary designates as an archaic term referring to "branches of polite learning, especially the ancient classics." Nowadays the term "the humanities" is broadened to mean nonscientific learning: history, literature, and philosophy; but there is still in its meaning something of its classical ontogeny.

Even then, the terms "the humanities" and "humane" have directly in common only that they both pertain to humans. When the Greek and Roman classics were written society was not humane; there was slavery, there was cruelty everywhere, in war, in law, in sport. Thoughtful, educated men could be only pessimistic about the realities of the world in which they lived. The Epicurean philosophy taught that if you do not attract the notice of the world it will not hurt you; wisdom is to withdraw to a quite private life with a few friends. For the Stoic all is predetermined; virtue is to choose in accordance with the divine plan, and

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if you do not choose you will have to anyway; nothing but this grim, if noble, virtue is of any value. Both philosophies rejected the world; both were philosophies of escape. The centuries and countries of the revival of the classical learning were not notably humane. Humanitarianism became the mode in society only in the nineteenth century, with the rise of liberalism, at a time when the classical learning and the obligatory study of the nonclassical humanities were in their decline.

Yet who of us has not hankered after the polite learning! If only our art of medicine were not so long and life so short! If only we had time for both! Our present-day notion of "liberal," as in a liberal education, is a Greek idea, connoting what is to be expected of a free man. Plato in the Laws distinguishes between two kinds of doctors, one a slave, the other a freeman.

> "The slave doctors run about and cure the slaves, or wait for them in the dispensaries—practitioners of this sort never talk to their patients individually or let them talk about their own individual complaints. The slave doctor prescribes what mere experience suggests as if he had exact knowledge; and when he has given his orders, like a tyrant, he rushes off with equal assurance to some other servant who is ill; ... But the other doctor, who is a freeman, attends and practices upon freemen; and he carries his enquiries far back, and goes into the nature of the disorder; he enters into discourse with the patient and with his friends, and is at once getting information from the sick man, and also instructing him as far as he is able, and he will not prescribe for him until he has first convinced him; at last, when he has brought the patient more and more under his persuasive influences and set him on the road to health, he attempts to effect a cure."

The latter is a philosopher's ideal physician. But this is based on physicians as they were to the degree that Greek statue represented a man as he actually looked.

Medicine of the Greeks

The Greek physicians of 430–400 B.C. were the fathers of modern medicine. It is only decent piety to try to understand them. There were two chief medical schools. Neither was in the great capital, Athens, but in the provinces, at Cnidos on the coast of Asia Minor, and at Cos off that coast. The physicians worked for a living; they could not have been rich, or an apprentice taking the Hippocratic Oath would not have sworn,

> "To hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money to share mine with him."

Greek medicine was the first intellectual discipline, and this was in the fifth century B.C., to abjure, not only superstition, but also general philosophic postulates and systematizing. The Coan author (430–420 B.C.) of "Ancient Medicine" began,

> "All who, on attempting to speak or to write on medicine, have assumed for themselves a postulate as a basis for their discussion—heat, cold, moisture, dryness, or anything else they may fancy—obviously blunder.... Wherefore I have deemed that [medicine] has no need of an empty postulate as do insoluble mysteries, about which any exponent must use a postulate, for example things in the sky or below the earth. ...For there is no test the application of which would give certainty. But medicine has long had all its means to hand, and has discovered both a principle and a method."

It was the Golden Age of Greece, the wonderful fifth century of boundless confidence and optimism that was soon to disappear from the Mediterranean for four centuries.

Both schools based their teaching on direct observation of cases and case histories. It is unfortunate and unfair that nearly all we know of the Cnidian school is from the criticism of it by its rival, the Hippocratic school at Cos. The author of the "Regimen in Acute Diseases," who may have been Hippocrates himself, begins

> "The authors of the work entitled Cnidian Sentences have correctly described the experiences of patients in individual diseases and the issues of some of them. So much even a layman could correctly describe by carefully inquiring from each patient the nature of his experiences. But much of what the physician should know besides, without the patient's telling him, they have omitted; .... And whenever they interpret symptoms with a view to determining the right method of treatment in each case... I censure them because the remedies they used were too few in number—purges and to drink whey and milk....
>
> The many phases and subdivisions of each disease were not unknown to some; ... but their account was incorrect. For the number will be almost incalculable if a patient's disease be diagnosed as different whenever there is a difference in symptoms, while a mere variety of name is supposed to constitute a variety of illness."

The Cnidians emphasized diagnosis, and carried differentiation to absurd lengths. They

used few remedies, which was certainly better at that time for their patients. One may imagine them as practical, unphilosophic, middle-class men, diligently comparing observations and puzzling over them, as one does when there is not to hand a workable hypothesis. The Cnidians, we may surmise, insisted on sticking to the facts of observation, nothing but the facts, and all the facts. They were on the straight road of science, but over two thousand years back.

The Hippocratic school was not so purely scientific. And it was the nonscientific impurity, probably, that has made its reputation throughout the centuries. Like the school of Cnidos, the school of Cos brushed superstition aside, and based itself on direct observation and the recording of case histories; but whereas the Cnidians emphasized the differences, i.e., diagnosis, at Cos they taught the unity in disease, they described the natural history of disease, as a pathologist today might write about inflammation in general. Their case histories show a close observation of signs and symptoms and their sequence, of the sputum and urine; these are recorded baldly, without inference. In their textbooks, as it were, they taught that diseases have a natural course, which the physician must know thoroughly in order to treat the patient properly and to be able to decide beforehand whether the patient will get well or die. For purposes of treatment and prognosis they did not, apparently, think it necessary to go further in diagnosis than to distinguish chest complaints, most commonly tuberculosis, and different kinds of malarial fevers. Diseases, they taught, are caused by a disturbance in the composition of the constituents of the body, by imbalance, disharmony. Nature tries to restore the balance, the harmony, which is health. *Vis medicatrix naturae* was the central Hippocratic doctrine. Nature may succeed or fail. All the physician can do for the patient is to remove by regimen all that may hinder Nature in her beneficent work of combating the disease. The notion of the crisis, the very word, was brought into medicine by Hippocrates.

For all their criticism that the Cnidians used too few remedies, the Hippocratics used hardly any more. They were fussier: the barley gruel had to be prepared just so; more or less fluid for the disease in this stage or that; there were rules about bathing, and so on. Both the patient and his family no doubt benefited from the exactly detailed care that was prescribed. Hippocrates stressed prognosis:

> "I hold that it is an excellent thing for a physician to practise forecasting. For if he discover and declare without being told, by the side of his patients, the present, the past and the future, and fill in the account in the gaps given by the sick, he will be the more believed to understand the cases, so that men will confidently entrust themselves to him for treatment. Furthermore, he will carry out the treatment best if he know beforehand from the present symptoms what will take place."

The case histories show, Plato's description of the ideal physician notwithstanding, that Hippocrates attended slaves as well as their masters; the case histories of both are recorded in the same manner. Hippocrates took into account the mental state of the patient:

> "She was silent and did not converse at all. Depression, the patient despaired of herself. There was also some inherited tendency to consumption.
>
> It was no longer possible to do her any good, and she died."
>
> In Thasos a woman of gloomy temperament, after a grief with a reason, without taking to bed, lost sleep and appetite, and suffered thirst and nausea. As night began there were fears, much rambling, depression and slight feverishness. Early in the morning frequent convulsions; whenever these frequent convulsions intermitted, she wandered and uttered obscenities; many pains, severe and continuous."

As one reads Hippocrates' case histories and his teaching, one feels a mind probing ceaselessly for correlations. One must take account (he insists) of the patient's symptoms, of course, but also the climate, the season, the weather, the sex, age, and diet. The temptation of a correlation is to believe it. Hippocrates believed some of his: that there are critical days in a disease, these are a fixed number, in some cases odd, in others even, when the battle between Nature and the disease reaches a climax—the crisis; diseases are connected with the seasons and the winds, and it is chiefly the change itself in the season which produces disease.

Where the Cnidians abjured all philosophy and dealt only with diseases, the Coans were distinguished by their philosophy, which was that

of Nature, and this led them to a doctrine of health. Health was Nature's way, disease was violence which Nature combated. Hippocrates taught what we call Hygiene, a regimen that preserved health: one must take account, not only of the kind of man a person is, but of what he eats and drinks, how he lives, and how the climate and seasons affect him. Hippocrates was the father of preventive medicine.

To Plato and Aristotle Hippocrates was "Mr. Medicine"; it was through them that his fame was perpetuated. Plato used the Hippocratic emphasis on "disease" rather than on "diseases" as a powerful example in his doctrine of essences, of the idea of a thing.

The Ionian philosophers, Hippocrates' predecessors, had conceived the univeral whole as Nature. Hippocrates brought it down to earth in his idea of Nature in a man's body. Nature was health: the right proportion, the right mixture, the right balance of opposites (Heraclitus). The doctrine appealed because it was optimistic: Nature was on our side—*Vis medicatrix naturae*—she would cure if given a chance. It was optimistic also because Nature's way was no dark secret, we could learn it. To Plato the physician was the model for the philosopher. For the Greeks, for whom culture of the body was an integral part of culture as a whole, it was an easy step from the special case of the health of the body to the general idea of spiritual health: harmony, the balance of opposites, hence symmetry, was Nature's way. Hippocrates' idea had still an additional appeal to the Greek philosophers. For them law was so wonderful an idea, it must be divine. Nature's way in the body, as Hippocrates saw it, was its purpose, its law. So from medicine, from our own most direct, personal experience we could learn Nature's law. From Hippocrates, Plato drew the Greek ideal of the golden mean, of proportion, which is health in mind, in body, in all things.

It is a noble philosophy. It was medicine's glory and a catastrophe for over 2,000 years; because medicine became inextricable from philosophy. From then until the end of the eighteenth century medicine was taught as some system, some dogma or other. It was as important, or more important, to be versed in rhetoric—a Sophist art—than to know the facts of medicine. There were few facts and many philosophies.

From the Greeks to the 18th Century

The centuries resounded with the arguments of contending dogmas of the schools. The Alexandrians surpassed the Greeks in anatomy, and some, drawing on their newer anatomic knowledge, insisted on nothing but mechanical explanations for all symptoms. Others, from the study of anatomy, and with no physiology, taught that it was useless to inquire into the causes of things; it is better to observe the facts and then do what one can; but observation of the facts and doing what one can was to juggle with analogies. No wonder a Pliny could brag that for 600 years the Romans got along very well without doctors. The drugs which they used were also superstitions. Galen's pre-eminence came from having read everything. He gave every phenomenon its name, every medical problem its solution. Drugs pertained to the hot, cold, moist, or dry, and one cured by opposites.

The medicine of the Arabs was little more than a retrograde gloss on Galen. Their real advance was in pharmacy and the therapeutic use of drugs; theirs was the first pharmacopoeia; they established the first apothecaries' shops. But their pharmacology was tainted with alchemy, and when it passed into the hands of the Europeans, it was mixed with witchcraft and magic.

Medicine then was book learning; educated laymen knew the names of famous physicians of the past and had a smattering of their doctrines. From the lay literature we can see how little medicine changed century after century. In the prologue to the Canterbury Tales we are told of the doctor

"...being grounded in astronomy,
He watched his patient's favorable star
And, by his natural magic, knew what
Are the lucky hours and planetary degrees
For making charms and magic effigies.
The cause of every malady you'd got
He knew, whether dry, cold, moist or hot;
He knew their seat, their humor and condition.
He was a perfect practising physician.....

He was well versed in Esculapius too
And what Hippocrates and Rufus knew
And Dioscorides, now dead and gone,
Galen and Rhazes, Hali, Serapion,
Averroes, Avicenna, Constantine,
Scotch Bernard, John of Goddesden, Gilbertine.
. . . he was rather close as to expenses
And kept the gold he won in pestilences.
Gold stimulates the heart, or so we're told,
He therefore had a special love of gold."

Chaucer's dates are 1340 to 1400. Sir Thomas Browne (1605–1682), some 250 years later, wrote

"the substance of gold was invincible by the powerfullest action of natural heat; and that not only alimentally in a substantial mutation, but also medicamentally in any corporeal conversion."

The thirty-seventh chapter of Montaigne's second book of essays has been an armory of assault weapons on medicine century after century down to Bernard Shaw. Montaigne was a sufferer of the stone when he wrote it; it was published in 1580.

"I see no kind of men," he wrote, "so soone sick, nor so late cured, as those who under the jurisdiction of Physicke . . ."

"No man unless he be a foole ought to undertake (purges). Cause a purgation to be prepared for your braine; it will be better employed under it than to your stomacke."

"A sick man was asked by his physician how he was. 'I have sweat much,' he said. 'That is good,' replied the physician. Another time the patient said he had a great cold and quivered much. 'That is very well,' said the physician again. On a third occasion the patient said he swelled and puffed up as if he had dropsy. 'It is not amiss,' the physician said. The patient exclaimed, 'I die with being too, too well.' "

"How many debates, doubts and controversies have they among themselves about the interpretation of urine."

Yet Montaigne protests that his best friends were physicians. "It is not them I blame, but their art."

In 1673 Molière's "Le Malade Imaginaire" appeared. Molière (1622–1673) was a dying man when he played in the first performances. The patient, Argan, has been imagining that he is ill, and wants his daughter to marry a physician so as to have a doctor in the family. Beralde, the brother of the invalid, is remonstrating with him:

"Beralde: He would dispatch you with the most implicit faith; and he would in killing you, only do what he has done to his wife and children, and what, if there were any need, he would do to himself.

Argan: What must we do then, when we are ill?

Beralde: Nothing, brother—Nothing. We must remain quiet. If we leave nature alone, she recovers gently from the disorder into which she has fallen. It is our anxiety, our impatience, which spoils all; and nearly all men die of their remedies, not of their diseases. [Montaigne]

Argan: But you must admit, brother, that this nature may be assisted by certain things.

Beralde: Good Heavens! brother, these are mere ideas with which we love to beguile ourselves. . . . When a physician speaks to you of aiding, assisting, and supporting nature, to take away from her what is hurtful and to give her that which she wants, to reestablish her and to put her in the full possession of her functions: when he speaks to you of rectifying the blood, of regulating the bowels and the brain, of relieving the spleen, of putting the chest to rights, of mending the liver, of strengthening the heart, of renewing and preserving the natural heat, of being possessed of secrets to prolong life till an advanced age, he just tells you the romance of physic. But when you come to the truth and experience, you find nothing of all this; and it is like those beautiful dreams, which on awaking leave you nothing but the regret of having believed them."

About a half century later, LeSage (1668–1747), the French dramatist and novelist, in his "Gil Blas" has a physician, Dr. Sangrado, thus instruct his new apprentice, Gil Blas:

"Bleeding and drinking water are the two grand principles; the true secret of curing all the distempers incident to humanity. Here you have the sum total of my philosophy. You are thoroughly bottomed in medicine [in three weeks] and may raise yourself to the summit of fame on the shoulders of my long experience. While I dose the nobility and clergy, you shall labor in your vocation among the lower orders."

The following is part of a conversation between Dr. Sangrado and one of his distinguished patients, the 70-year-old Canon of Valladolid Cathedral,

"The question here is to remedy an obstructed perspiration. Ordinary practitioners in this case would follow the old routines of salines, diuretics, volatile salts, sulfur and mercury; but purges and sudorifics are deadly practice. Chemical preparations are edged tools in the hands of the ignorant. Your usual diet? 'I live pretty much on soups,' replied the canon, 'and eat my meat with a good deal of gravy.' Soups and gravy!" exclaimed the petrified doctor, "Upon my word it is no wonder you are ill. High living is a poisoned barb, a trap set by sensuality to cut short the days of wretched

man. We must have done with pampering our apetites: the more insipid, the more wholesome. The human blood is not a gravy!. . . ."

Smollet translated LeSage. In his "Roderick Random" there are physician-surgeons who belong in the dreadful pictures of Hogarth.

Bernard Shaw's "The Doctor's Dilemma" belongs in this group, even though when it was written in 1906 it was more than a century out of date. The criticism of doctors in this play is that of Molière in "Le Malade Imaginaire" in twentieth century terms.

The foregoing quotations are probably unfair to the doctors of their time. Nevertheless, one is struck by their sameness. It must be that doctors' language and method of treatment changed very little from the Middle Ages through to the end of the eighteenth century. Every physician, good or bad, had a philosphical system by which he treated his patients, and he held to it, come what may, to the bitter end—of his patients. The worst of these physicians were charlatans, the best were quacks, and the more sincere the quack, the more dangerous he was to the patient. Medicine, as a therapeutic art, was, in the main, premature until the end of the nineteenth century. But doctors might have done better by their patients, for all the paucity of their facts, and their misconceptions, if they had not been obsessed by their systems. Systems such as theirs were bad medicine because they were constructions into which the physicians forced their patients. Systems which claimed to explain everything did not encourage observation of new facts.

Surgery in the Early Centuries

Surgeons were more highly thought of as healers because they were more down to earth and more successful, even though their social status was lower. The physicians were differentiated from surgeons from very early times. Asklepios, whom Homer calls "the good leech," had two sons, Machaon, a surgeon, and Podalirius, evidently a physician. Homer called Machaon "Shepherd of the Host," and when Machaon was wounded before Troy (doctors fought then), Idomeneus, a famous, tough spearman, urges Nestor quickly to get Machaon to the ships.

"For," he says, "a leech is worth many other men, to cut out arrows, and spread soothing medicaments."

All that one finds said of Podalirius is that he had the gift from his father of recognizing what was not visible to the eye and tending what could not be healed. There is no record of anyone saying that the physician son of Asklepios was "worth many other men." There is a puzzling passage in the Hippocratic oath:

"I will not use the knife, not even, verily on sufferers from stone, but I will give place to such as are craftsmen therein."

Nowhere else in the Hippocratic literature is a physician prohibited from use of the knife. Indeed there are references to physicians doing surgical operations. The Hippocratic books dealing with fractures and dislocations are, by modern standards, by far the best. From Hippocrates on, a physician was a learned man, he had book knowledge and philosophy, and the Greek, upper class disdain of manual labor; the Oath refers to surgeons as craftsmen. Scattered references and the long lineage of barber-surgeons suggest that surgeons were a lower class than physicians. Paré (1510–1590) began as a barber-surgeon, and after he became famous wrote his books in French, not Latin. He was opposed by the faculty of medicine even though he was held in the greatest esteem by several kings and the army. The same writers who jeered at physicians were respectful of surgeons. Thomas Dekker in 1625 dedicated one of his books

"To the noble gentlemen, Mr. Thomas Gilham, Chirurgian. I honour your Name, your Art, your Practice, your profound Experience."

Montaigne in full blast against medicine, wrote of surgery,

"Whereby I judge the arte of Chirurgery much more certaine; for it seeth and handleth what it doth; and therein is less conjecture and divination."

For all the greater respect accorded the surgeon as a healer, he did not come up to the physician socially until the end of the eighteenth century. A surgeon said of John Hunter (1728–1793): "More than any other man he helped to make us gentlemen." Physicians had the classical learning, by this they were gentlemen,

even if as healers they were considered inferior.

The Rise of Modern Medicine

It would take too long to even touch on the rise of modern clinical medicine beginning with Sydenham (1624–1689) and Morgagni (1682–1771.) Fundamental changes in outlook did not start until the end of the eighteenth century, although the knowledge had been accumulating for nearly two centuries. Vesalius (1514–1564) and Fallopius (1523–1562) had built the foundations of our modern anatomy in the sixteenth century; even Harvey's discovery of the circulation of the blood in 1628 had little effect on medicine for a long time. Malpighi (1628–1694) from the 1660's onward saw the capillaries with his compound microscope, the histological structure of lung, kidney, and glands; he described the developing chick embryo. Leeuwenhoek (1632–1723) was less systematic, more of an amateur microscopist; but he saw and drew muscle fibers, blood corpuscles, spermatozoa, and bacteria. Yet medicine lagged behind physics and astronomy; because the leaders in medicine were still striving for complete systems in the classical manner; and dazzled by the grand generalizations of astronomy and physics, they wished to do likewise in medicine.

A title to this part of my lecture might have been "Our Forefathers: Guides, Mentors and Bad Examples." The fault was not only that they knew so little, but the philosophical posture kept them from learning. The classical philosophies were dogmas. Dogma is static. It is in the very nature of dogma that it claims more than it has a right to. No wonder independent spirits among the writers reviled physicians.

In the Book of Genesis is stated:

> "God made the beast of the earth after his kind, and cattle after their kind, and everything that creepeth upon the earth after his kind: ...."
>
> And God said, "Let us make man in our image, after our likeness: and let them have dominion over the fish of the sea, and over the fowl of the air, and over the cattle, and over all the earth, and over every creeping thing that creepeth upon the earth."

God in his infinite wisdom encompasses all creation; He comprehends all the wonderful, infinite diversity of the world; He understands all. But when man tries to understand, all he can do is to simplify by stripping off and casting aside all that makes for individual difference. In this simplification the phenomenon is belittled, it is cut down to the size of man's mind. For example, there is little structural difference between the steroid male and female hormones, testosterone and estrone. The whole difference between the two is transposition of hydroxyl and ketonic groups and two more double bonds in the first ring of the female hormone, estrone. It need not be stressed that there is more to the differences between man and woman.

Herein is the root of the canker that classical philosophy was for medicine. Plato taught, for example, that all tables had in them the essence of tableness. This essence is the truth, the differences in shape and materials are accidental and unimportant. As an example he took Hippocrates' teaching: "disease" is what is important, not "diseases"; disease, is, essentially, always the same, the differences are accidents of form like the shapes of tables. What does not fit into a classical system is left out, is not seen. It is at most an irritating irrelevance. A sick human being becomes a case.

It is illustrative that an early European writer such as Chaucer made fun of a doctor's show of learning, his vanity, his greed, but he respected the doctor's ancient authorities and believed in his medicines. Even a Rabelais lectured on Galen and Hippocrates. There is a different temper in the writers that came with and after the Reformation. The intellectual leaders of the Reformation, Erasmus, More, and Montaigne, revolted against the intellectual authoritarianism of the religious and philosophic systems of Rome; they did not abjure the hierarchy of the Church. And so, in the quotations above from Montaigne, Moliere, and LeSage, the attack (and a savage one it is) is on the pretensions of medicine practised as one philosophical system or another. The Reformation was the revolt of the individual against the authority of system, whether in religion, politics, art, or literature. The sick writer wanted his own illness treated, and had no concern for the system, no matter how learned. He could have found authority for this too in Hippocrates.

"The art has three factors," wrote the author of "Ancient Medicine," the disease, the patient and the physician. The physician is the servant of the art. The patient must cooperate with the physician in combating the disease."

Of course Hippocrates did not know that each foot stood on a different road that led to two vastly different countries. Who can see so far? Two thousand years later, even a Sydenham, who strove to study disease without preconceptions, and without necessarily explaining the disease (in this he was more Cnidian than Hippocratic), said:

"Disease is an effort of nature to restore the health of the patient by the elimination of morbific matter."

Sydenham took Hippocrates as his model, the "natural history of disease," *Vis medicatrix naturae*, and all. A Sydenham could borrow all Hippocrates' words, but the forces that gave a doctrine of a bygone age its life could not be borrowed; they were spent. The fifth century B.C.—the seventeenth century A.D.? No. An idea to come again must be born in a new incarnation.

But we cannot think, we cannot see much without an hypothesis, a theory, a system. If systems are bad, and yet we cannot get along without a system, what are we to do? The writers of the Reformation were aware of the difficulty. The answer in religion, Erasmus proposed, is that every man must make his peace with God by himself. Montaigne gave the general answer, which is a basis for all empirical philosophy. (He would have hooted at a statement about him such as I have just made.) When he was asked for advice on the education of a young kinsman, he wrote:

"The bees fly about here and there among the flowers, and from what they cull they make honey, which is all their own, neither thyme nor marjoram. So of pieces [of learning] borrowed of others, he may alter, transform and mix them, to shape out of them a piece of work all his own."

Montaigne is our philosopher. He noted:

" 'Amongst so many millions of men, you shall scarce meet with three or four that will daily observe and carefully keep a register of their experiments. Physicke is grounded upon experience and examples.' He said with tongue in cheek, 'So is mine opinion. Is not this a manifest kinde of experience and very advantageous.' "

Montaigne's advice was to get the facts, all you can, but the facts, and then shape something out of them all your own. What could this mean in medicine? Make a theory, a general picture of a disease, and overall pattern. Superimpose on it and have stand out from it, the individual, both in contrast with the pattern and blending with it. To see the particular in the general is to catch life. Of course this is what the good physician does all the time; it is what we mean by "judgment." It is to treat a sick person as an individual human being, and not as a case in a statistic.

The Patient in Modern Medicine

Our scientific medicine is a system too. Unlike our forefathers, we admit we do not know everything. But the establishment of the "Franz Groedel Memorial Lecture" testifies to the concern of the American College of Cardiology that in our scientific system, for reasons inherent in it and in our present society, there is danger that the result may be the same as in the former philosophical systems of medicine, in that the patient may be degraded from a human being to a case, to the detriment, humanity apart, of the good treatment of the patient. The problem has arisen out of the great scientific progress in medicine. Modern science, being what it is, entails specialization. Specialization is fragmentation. Instead of, as in systems of the past, making the mistake of seeing only the general, there is danger of seeing only separated aspects of the patient according to the specialty, of fragmentation of the patient. What are we to do?

Of course there is no turning back from scientific medicine, from specialization. The famous first aphorism of Hippoerates holds for us:

"Life is short, the Art long, opportunity fleeting, experience treacherous, judgment difficult. . . ."

The development of psychology (another specialty) has led us to see that a person who is ill may undergo important changes in his outlook and personality, and that these changes need to be taken into account in treating him. The danger in the very success of psychology (and psychiatry) is that care of the patient as a human being will become a specialty. Are we to send every patient to a psychiatrist to have

this aspect of his illness looked after, as we send him to a radiologist for x-ray diagnosis or treatment? The psychiatrist is trained in these matters, why should he not be used as other specialists are? This is the way to dehumanize medicine completely.

Yet, how is the patient to get the benefits of all that modern medicine has to give him? There are the many interrelated problems of patients not having enough money, of doctors not having enough time, of there not being enough doctors, of the possibility that doctors may not be getting the right education for our time. All the pressures of modern life are toward standardizing us: "It is cheaper and more efficient this way," they tell us. And yet we know that the best medicine is to treat the patient as an individual.

Medical Education and Specialization

You know these problems better than I do. Probably no one of these problems can be solved separately. I beg your indulgence to make a few comments on what might be done in the way of the education of the doctor. The doctor's task requires sympathy and scientific knowledge. By sympathy I do not mean feeling sorry for the patient or his family; that, surely, we may take for granted. The sympathy I mean is insight into how the patient feels and thinks, in short, to understand him as a person, before and during his illness and what he may be like afterward. This is the art of medicine. Our great engineering works are often also fine works of art. How beautiful are the great new bridges, the mountain roads, and the dams! It will be sad if medicine ever ceases to be an art and becomes only science, solely a matter of test, technic, and prescription by IBM machine. I believe that sympathy can be fostered, that it can be taught. I know it will be objected that the sympathy I mean is like the feeling for poetry or the state of grace, that it is a state of grace. Yet, throughout the ages the state of grace has been taught, a feeling for poetry is fostered: it is done by indirection, by the study of noble examples, and by the luck of having a good teacher. Surely it needs no pleading that it is good for the student to know critically as well as sympathetically, the ideas, feelings and actions of the great men of the past. The study of the humanities predisposes to sympathy.

We need sympathy also in a broader historical sense: to apprehend the different systems of values by which men lived. Let me give you a recent example of how scientific concepts were formed by society's needs. The steam engine dominated nineteenth century Europe. In order to make better steam engines the science of Thermodynamics arose. Its name connotes steam engine, its terminology even today is of the steam engine. Incidentally, the first law of Thermodynamics was discovered by a physician, Mayer, and first given its mathematical exposition by another physician, Helmholtz. Thermodynamics dominated all nineteenth century science. Physiologists, not thinking very much and overawed, probably, by their physicist colleagues, taught that the animal body was like a steam engine, with a stable structure that suffered only slight frictional wear and tear, which was replaced from a small part of the food, and that the bulk of the food was the fuel. Hence the terms "endogenous" and "exogenous" metabolism. This is an entirely unbiologic concept. It is now proved that there is no utility in distinguishing between fuel and structure. Some ostensibly stable structures are breaking down and rebuilding very fast. Half the liver protein in a healthy adult is new every week. Muscle, including cardiac muscle, is breaking down and rebuilding more slowly than liver, but, nevertheless, it too is in a dynamic state. A living thing is not like an engine, it is not like anything else, it is only like a living thing.

To return to my theme of the value of having students specializing in science also learn nonscientific subjects, I would draw your attention to the fact that in some of our leading engineering schools 25 per cent of the undergraduate curriculum is devoted to the humanities. This has been done for about a quarter of a century, and the consensus of opinion is that it is good.

On the scientific side, it seems to me that what the modern medical student needs to be taught is how to be, as it were, an administrator of all the medical specialties. It is not good, I believe, to teach the subjects of undergraduate

medicine as introductions to or pseudo preparations for research in these subjects. It may be that what I have in mind would be best in graduate medical instruction. I have in mind somebody like the administrator of a great department of government, more nearly as in the British government than ours. The head of the department need not be, often is not, a specialist. He was chosen in the first place on the basis of his record at college. He has the kind of mind that can use the knowledge and advice of specialists; he can put it all together, he has the judgment to shape it into a possible policy, which he then presents to his cabinet minister, who takes the responsibility for it. I believe it would be possible to train a doctor so that he could appraise critically the findings of all the medical specialties, including psychiatry, and base treatment upon that knowledge. My proposal entails a reversal of the medical hierarchy, with the general practitioner at the top and the specialists below him. I believe that it could be worked out so that even less than brilliant minds could be taught to practise medicine in this way. Such men would prevent the fragmentation of medicine by specialization, as the clinical pathologist, aided by the roentgenologist, has done in the past.

We in medicine are involved in the general problem of our time of keeping up with the very rapid progress of science, the problem of finding a way for the healthy assimilation of the flood of new and often strange scientific knowledge into the life of society. In medicine there is, I think, a better chance of our solving our part of the problem than in other branches of science. The drive to do so is felt more directly because the need impinges directly on the individual, on his freedom from pain and disability, on his chances of living or dying. And the doctor is, I think, more broadly trained within his discipline, relatively, than the engineer, the physicist or the chemist. There is an opportunity for medicine to give a lead, and there is a chance that the consequences may not be as bad as was the lead Hippocrates gave to Plato and Aristotle.

A few weeks ago I was at a symposium on the subject of sickle cell anemia. Among the participants were clinicians, pathologists, chemists, physicists, and geneticists. The findings of an anthropologist and of an epidemiologist were cited: malaria is involved in the persistence of sickle cell anemia. Some of us felt it was a pity that the anthropologist and epidemiologist were not personally invited. Anthropology, the *logos* of man, it would seem is a proper subject for the medical student; and geography too. We are returning here, in principle, to a teaching of Hippocrates.

In the argument over the hydrogen bomb are clinicians, radiologists, geneticists, physicists, the military, politicians, and those with the responsibility of government. Just now it is more an argument than a discussion in which men of different points of view try to understand each other and come together.

Obviously, it would be wrong to describe present day science, let alone present day medicine, as being altogether like the astronomers' picture of our expanding universe, with all its different disciplines moving farther and farther apart in chaos. They can be, they have been, here and there they are brought together, and out of them is shaped "a piece of work all [its] own." But this does not happen by itself. We have to will it, to go out and seek situations and means of doing it, to foster the purpose in our teaching. In medicine there is a choice in several senses as to whether to practise as an isolationist or as part of the entire world.

In the long bibliography of Franz Groedel there is a paper of 1929 entitled "Heart Disease and Modern Life—A Preachment to the Profession and the Public." The paper begins:

> "It is not rational for the heart patient to lose hope—the most important cause [of heart disease] is modern life. A good method [of treatment] is to go away from home for some weeks or months—to go to a place which is especially adapted for the treatment of overworked people."

He recommended Bad Nauheim.

> "It is not only the Nauheim cure which will help a patient; if the patient has a will to become healthy and if the physician understands to prescribe individually the treatment according to personal circumstances, nearly every heart case may be improved or cured."

I believe that Franz Groedel knew the following passage in Montaigne on cures at spas such as Bad Nauheim.

"I have by occasion of my travels seene almost all the famous Bathes of Christendome and some years since have begun to use them: —I have as yet found no extraordinary good or wondrous effect in them—Yet have I seene but few or none at all who these waters have made worse—and no man can without malice denie, but that they store up a man's appetite, make easie digestion.... Whosoever goeth to them, and resolveth not to be merry, that so he may enjoy the pleasure of the good company resorts to them, and of the pleasant walks or exercises, which the beauty of those places where bathes are commonly seated doth affoord and delight men withall; he without doubt loseth the better part and most assured of their effect...."

Dr. Groedel's paper concludes with a quotation from Hippocrates, from "Airs, Waters and Places." His preachment in this paper is according to Hippocrates' precept for the good physician.

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Historical Milestones

Pulmonic Stenosis with Patent Interatrial Septum (Morgagni, 1761)

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THE CLINICOPATHOLOGIC conference has come to be regarded as a pedagogic method characteristic of American medical schools. Conferences of this type are now standard pabulum in third and fourth year classes, in graduate courses, at medical meetings, and in medical journals.

Probably the immediate impulse for the present great development of these conferences came from the late Richard C. Cabot of Boston, whose famous "Cabot Cases" have appeared in the *New England Journal of Medicine* for so many years. It may be remarked, with great regret, that many present-day students are unaware of Dr. Cabot's other important contributions to American life, most especially his contribution to the development of "social service" in hospitals.

Whatever New England genealogists may think, the ancestor of Cabot was Giovanni Battista Morgagni (1682–1771), at least as far as the art of clinico-pathologic correlation is concerned. Morgagni's immortal *De Sedibus et Causis Morborum Per Anatomen Indagatis* (Concerning the Locations and Causes of Diseases, Investigated by Dissection) is a huge collection of what might be called eighteenth-century Cabot cases, systematically arranged according to the geographic regions of the body, and then subdivided according to symptoms. Thus the five books, published in sumptuous format at Venice in 1761, deal respectively with (I) diseases of the head, (II) diseases of the thorax, (III) diseases of the abdomen, (IV) surgical and generalized diseases, and (V) addenda. Book I, on diseases of the head, treats successively of headache, apoplexy, other soporific diseases, phrenitis, etc.

For the special delectation of readers of THE AMERICAN JOURNAL OF CARDIOLOGY we publish herewith a case of pulmonic stenosis with patent interatrial septum. This is taken from Book II, Letter the Seventeenth, which, in the translation of Benjamin Alexander (London, 1769), bears the title "... of Respiration being injur'd from Aneurisms of the heart, or the Aorta, within the Thorax".[1]

It must be remembered that at this time the term aneurysm included not only circumscribed dilatations of blood vessels but also embraced cardiac dilatation and hypertrophy. This is seen, for example, in Lancisi's *De Aneurysmatibus*.[2]

The reader is requested to observe (a) that the case is recorded under the heading of dyspnea, which is the theme of Morgagni's Letter the Seventeenth; (b) that the clinical history is of utmost simplicity and clarity; (c) that there is no mention of physical signs, the art of physical diagnosis being as yet poorly developed; (d) that there are no laboratory reports; (e) that there is no mention of antemortem diagnosis, although the patient's physician perhaps had formulated at least a crude hypothesis to account for the symptoms; (f) that the anatomic findings are described clearly;

(g) that although microscopes were then in existence, microscopic pathology was virtually non-existent; (h) that Morgagni skillfully deduced the character of the hemodynamic disorder by observing the anatomic malformation.

Morgani's Case Report

A virgin who, from the very time of her birth, had always lain sick, especially on account of her very great debility, breath'd short, and had her skin ting'd all over with a kind of livid colour; at length, when she came to be about sixteen years of age, she died. She had a heart that was very small, and towards the apex, in a manner roundish. The right ventricle was of the form that the left generally us'd to be, and the left of the same form that the right us'd to be; and although the right was wider than the left, yet it had thicker parietes. The right auricle, in like manner, was universally enlarg'd, and twice as big as the left, and twice as thick; betwixt the two, even then, the foramen ovale was open, so as to admit the little finger. Of the three triangular valves, one had a proper bigness, the two others were less than usual. The sigmoid, which lie at the mouth of the pulmonary artery, were at their basis indeed natural, but in their upper part seem'd cartilaginous, nay indeed they had already a small ossification; and were so connected together in this part, that they did but just leave a little foramen, not bigger than a barleycorn, through which the blood was sent out. And at this foramen also were some small, fleshy, and membranous productions, plac'd in such a manner, that they might supply the places of valves, by yielding to the blood that was going out, and by resisting that which was about to return.

I should suppose that this virgin had the beginnings of that disorder at the mouth of the pulmonary artery, from her original formation; to which disorder, being gradually more and more encreas'd, every thing she suffer'd when living, and what were found in the dead body, are without doubt to be referr'd: that is to say, the less quick, and less ready entrance of the blood into the artery, from this cause, was a reason why, on the one hand, a less quantity of it should be transmitted through that artery and its corresponding vein, to the left auricle and left ventricle, and from this should be sent to the whole body; and, on the other hand, that a greater quantity of blood than is natural should remain in the right ventricle, right auricle, and all the veins. From whence the colour of the whole skin, in a manner livid, and the dilatation of the right ventricle and right auricle, and the continu'd communication by the foramen ovale, by reason of its valve being urg'd towards the left side, by the great quantity of blood from the right, whereas but little urg'd it on the left side, and applied it to the edge of the foramen. But, for contrary reasons, the auricle and left ventricle were neither sufficiently open'd out and dilated, nor sufficiently strong, and the proper influx of blood to the brain, and to all other parts, being deficient, that very great debility, and difficult respiration were the consequences; and these even for that very reason, because from the small portion of blood entering into so large and firm a vessel as the pulmonary artery, it could neither be sufficiently expanded, and dilated, nor consequently contract and restore itself, as it ought to do, in order to carry the blood properly through the lungs.

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Diagnostic Shelf

Atrial Septal Defect

Intracardiac Phonocardiography

THE PATIENT,* a 16-year-old boy, entered the hospital for cardiac study. A heart murmur had been found on routine examination at the age of 14. He had practiced sports without difficulty. There was no history of cyanosis, peripheral edema, epistaxis, or joint pains.

grade 2–3 systolic murmur over the 2nd and 3rd left interspaces. P_2 is loud and split.

Electrocardiogram: Complete right bundle branch block. Right ventricular hypertrophy.

Phonocardiogram: Diamond-shaped systolic pulmonic murmur. Split P_2.

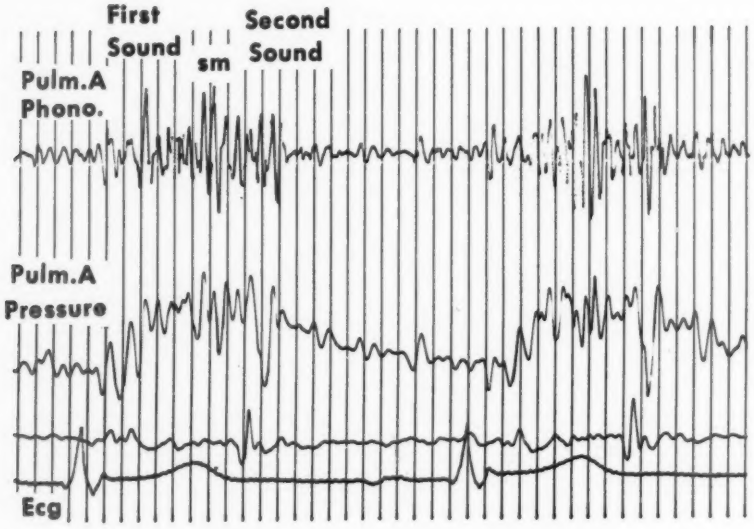

Fig. 1. Simultaneous phonocardiogram and pressure curve obtained from the pulmonary artery.

Physical Examination: A well developed, husky youngster, weighing 186 pounds. Blood pressure 128/70. Pulse 72, regular. No cyanosis or clubbing. The jugular veins are not distended. The heart is slightly enlarged to the left, and the base of the heart is widened, with dullness in the 2nd–3rd interspaces. There is a

* Private patient of Dr. O. M. Haring, Chicago, Illinois.

Clinical Impression: Atrial or ventricular septal defect.

Cardiac Catheterization: A step-up of oxygen content was found from the superior and inferior cavae to the right atrium. The left-to-right shunt was measured as twice the volume of aortic flow (PA = 12 *l*/min; Ao = 3.9 *l*/min). Right atrial, right ventricular and pulmonary pressures were normal.

Intracardiac Phonocardiograms (Fig. 1): Pulmonary artery: large vibrations during systole. Right atrium: only a few vibrations in late systole and early diastole.

These data confirmed the diagnosis of atrial septal defect.

Discussion

This case presented an interesting problem. A strong athlete with no complaints was examined and a murmur was found. The existence of right bundle branch block and of a loud systolic pulmonic murmur led to the diagnosis of atrial septal defect. This diagnosis was confirmed by catheterization which revealed an atrial shunt which was twice as large as aortic flow.

The intracardiac phonocardiogram revealed that the murmur was a "flow" murmur created within the pulmonary artery.

The split second sound was explained as due to the bundle branch block (normal right ventricular pressure) plus, possibly, the effect of increased output of the right ventricle. The mechanism of production of the systolic murmur of similar cases has been the subject of discussion. Apparently, those who advocated a "flow" murmur were correct, in contrast to others advocating more complex mechanisms.

This case illustrates a frequently observed fact: that the pulmonary circulation can accommodate an enormous amount of blood as long as no functional contraction or structural damage of the arteries occurs to increase the resistance. On the other hand, any, even small, narrowing of the pulmonary vessels leads to severe hypertension of the main pulmonary artery and right ventricle in the presence of increased flow.

A. A. Luisada
M. R. Testelli
Chicago, Illinois

Readers are invited to submit reports of interesting cases and illustrative tracings for this department. These should not exceed 1,000 words in length. Although not necessarily original, all material submitted should have teaching value.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Query: What are the benefits of the use of narcotics in myocardial infarction?

Answer: In addition to the primary aim of relief of pain, the administration of narcotics to patients with acute myocardial infarction has two other important objectives: The first is that of preventing complications due to reflexes which may be operative in promoting cardiac arrhythmias, shock, and cardio-pulmonary complications. The second objective is the reduction of the work of the heart, an important aim in the treatment of coronary patients. This is why one sometimes should continue the use of narcotics for a long time, depending upon the condition of the patient. In other words, narcotics are given to prevent complications and to insure maximum rest of the heart.

Query: What are the possible dangers in the use of narcotics in myocardial infarction?

Answer: In the presence of low blood pressure one must be careful of the dosage. Unfortunately, this applies particularly to morphine. In general, these drugs decrease venous return to the heart and if there is danger of impending shock the lowered blood pressure may precipitate it. This means that one must use caution in the dosage and should check the blood pressure frequently, especially before each dose. Physicians who have had experience with intravenous administration of morphine in coronary patients have reported occasional instances of sudden death precipitated by the injection.

Query: What are the possible dangers in the use of Isuprel® in coronary patients?

Answer: Isuprel is a newer drug which has been used most frequently in patients with bronchospastic disease, and now is also used in the treatment of heart block. The pharmacology of the drug is still not completely known. In animal experiments it has been observed that isuprel causes a drop in aortic pressure and, at the same time, a marked rise in pulmonary pressure. This is usually of short duration in normal animals; it may not be so in cardiac patients. Therefore, in the presence of pulmonary congestion the use of isuprel may not be entirely safe. The same applies to the danger of shock. If the blood pressure is very low, isuprel might precipitate shock by further lowering the systemic blood pressure.

Query: What is the value of alcohol vapor treatment in pulmonary edema precipitated by acute myocardial infarction?

Answer: Alcohol vapor with oxygen has been found extremely helpful in the symptomatic treatment of pulmonary edema in coronary patients. It is not to be considered a basic method of treatment. It only helps mechanically by decreasing the amount of foam in the bronchial airways and thereby helps the patient to breathe and to receive oxygen. In cases of myocardial infarction alcohol vapor treatment has been given for hours and sometimes for days. One should take the precaution of starting with a small alcohol vapor flow, increasing gradually as the tolerance increases and discontinuing the flow for several minutes every half hour. The usual plan is 20 minutes of treatment with oxygen alcohol vapor and 10 minutes of plain oxygen, thereby preventing any toxic reactions from the alcohol.

Query: Does digitalis given to patients with acute myocardial infarction increase the incidence of or predispose to atrial and ventricular arrhythmias?

Answer: Digitalis may cause ventricular arrhythmias in patients with myocardial infarction, recognized as such by their characteristic patterns in the electrocardiogram. More rarely

it may cause atrial arrhythmias, particularly atrial fibrillation. Such arrhythmias are generally rare unless very large doses of digitalis are used. In older patients, however, ventricular arrhythmias may appear with relatively small doses, even with only one tablet a day. If digital is given in a sensible way and the "full dose" treatment avoided, then cardiac arrhythmias caused by digitalis are rare.

Query: What is the value of papaverine, atropine, and magnesium sulfate in the treatment of ventricular tachycardia?

Answer: Papaverine is useless for this purpose. Atropine is also valueless. Magnesium sulfate is excellent for treating ventricular tachycardia not due to coronary occlusion. In the presence of myocardial infarction, however, one should hesitate to use a drug like magnesium sulfate which may further damage the myocardium.

Query: Is postscarletinal pericarditis considered to be a rheumatic manifestation or a benign pericarditis?

Answer: Fever, arthritis, pericarditis, and carditis may follow in the wake of scarletina. It is indistinguishable from, and presumably identified with, rheumatic fever.

Query: Can the fluid in nonspecific pericarditis be bloody in the absence of tuberculosis?

Answer: Pericardial fluid in nonspecific pericarditis may be bloody in the absence of tuberculosis or malignant tumor. Grossly hemorrhagic effusions must be differentiated from hemorrhage into the pericardium due to a dissecting aneurysm, ruptured myocardial infarct, and hypoprothrombinemia.

Query: Can S-T changes without T wave changes occur in mild pericarditis, returning to normal in about one week?

Answer: Typical electrocardiographic changes are not invariably present in pericarditis. S-T changes may be transient and frequently show considerable variations from day today.

Query: Would inverted T waves and isoelectric S-T segments observed 36 hours after onset be strong evidence in favor of the diagnosis of myocardial infarction rather than acute pericarditis?

Answer: Myocardial infarction cannot be differentiated from nonspecific pericarditis from the appearance of the T wave. Serial changes in the tracings recorded from day to day and week to week will make the differentiation. In pericarditis the QRS complex remains normal, reciprocal depression and elevation of the S-T segment in leads I and III are uncommon.

Query: Have acute phase reactions been studied in the postmyocardial infarction syndrome and what have been the results?

Answer: In the cases studied, the tests were positive.

College News

AIMS OF THE COLLEGE

The American College of Cardiology established in 1949 as an organization of physicians and scientists of good will and high standing is dedicated to the following purposes:

(1) To promote and advance the science of cardiology and angiology, and the study and treatment of cardiovascular disease

(2) To cooperate with other organizations, practitioners and scientists dealing with the same or related subjects

(3) To arrange for mutual meetings of cardiologists and angiologists, with scientists interested in cardiovascular physiology, anatomy, pathology, pharmacology and allied sciences

(4) To make available postgraduate training in cardiology, angiology, and cardiovascular disease

(5) To foster and encourage centers for study, treatment, and research of the cardiovascular system

(6) To edit, publish, and sponsor publications pertaining to cardiology, angiology, and cardiovascular diseases

(7) To promote public welfare by education and aid in the prevention and treatment of cardiovascular diseases.

(8) To arrange meetings of clinicians, basic scientists, cardiovascular surgeons, and specialists in fields related to cardiovascular diseases.

ELECTION INTO THE COLLEGE

Election into the College is by invitation of a College Governor or Fellow. The Secretary's office sends application blanks and instructions to the nominating sponsor. These instructions contain the minimum eligibility standards for the various grades of membership in the College. Information regarding these requirements and other College matters are available from the office of the Secretary, Empire State Building, New York 1, N. Y.

OFFICERS OF THE COLLEGE

The officers of the College for the year 1957–58 are as follows:

President . . . . . George R. Meneely, M.D., Nashville, Tenn.

President-Elect . . . . . George W. Calver, M.D., Washington D. C.

Vice-Presidents . . . . . Osler A. Abbott, M.D., Emory University, Ga.
Myron Prinzmetal, M.D., Beverly Hills, Cal.
Herbert Eichert, M.D., Miami, Fla.

Secretary-Treasurer . . Philip Reichert, M.D., New York, N. Y.

Assistant Secretary . . . Hannibal De Bellis, M.D., New York, N. Y.

Assistant Treasurer . . Louis F. Bishop, M.D., New York, N. Y.

SEVENTH ANNUAL MEETING

The Seventh Annual Meeting of the College will be held May 20th to 24th, 1958 at the Chase-Park Plaza Hotel in St. Louis, Missouri.

The scientific program will consist of Symposia, Panel Discussions, "Fireside Conferences," as well as special lectures. The topics to be discussed include:

(1) Metabolism of the Myocardium

(2) Cardiac Hypertrophy

(3) Present Management of the Tetralogy of Fallot

(4) End results of Surgery of Aortic Stenosis

(5) Effect of Exercise and Physical Stress on Cardiac Function

Members of the College are invited to submit abstracts limited to 300 words covering original work in the field of cardiovascular diseases to the Chairman of the Scientific Program Committee, Dr. John S. LaDue, 115 East 61st Street, New York 21, N. Y., prior to January 25, 1958. One or two scientific sessions will be devoted to the presentation of these papers.

Additional features of the convention will be the scientific and technical exhibits, the annual business meeting, the banquet and visits to nearby medical facilities. Fellowship certificates will be conferred at the convention. An entertainment program for the ladies is being planned. Details of the program will be published in the JOURNAL.

Space for the technical exhibits has been almost completely assigned. There are still booths available for suitable scientific exhibits. Physicians who are interested should write to Dr. Seymour Fiske, General Convention Chairman, 150 East 71st Street, New York 21, N.Y.

Hotel reservation forms will be mailed to the College membership and should be returned promptly. The local Convention Arrangements Chairman is Dr. Edward Massie, 457 North Kingshighway Boulevard, St. Louis 8, Missouri.

Progress Notes in Cardiology

A section devoted to *Progress Notes in Cardiology*, edited by Dr. Emanuel Goldberger, will be included in future issues of the JOURNAL. Investigators and research workers are invited to submit to the editor, with a view to publication in an early issue, résumés of work in progress or recently completed.

Announcements

International Conference on the Pulmonary Circulation

The Chicago Heart Association is sponsoring an International Conference on the Pulmonary Circulation to be held at the Palmer House, Chicago, Illinois, March 20–22, 1958. Approximately 30 authorities will discuss the physiology and pathology of the pulmonary circulation and the changes occurring in primary lung disease and in congenital and acquired heart disease.

Information pertaining to program participants and registration is available from the Chicago Heart Association; Dr. Wright Adams, Chairman, Symposium Planning Committee, 69 W. Washington St., Chicago, Illinois.

Home Study Courses in Electrocardiography

The University of Southern California School of Medicine announces two home study courses in electrocardiography.

The basic course is designed to offer instruction to the beginner in ECG interpretation as well as to the physician who requires further training in fundamentals. Every week for one year, the Postgraduate Division will mail a lesson to the enrollees. Each week, a particular subject, such as, ventricular hypertrophy, bundle branch block, myocardial infarction, etc., will be discussed and exemplified by ECG tracings. More important, "unknown" ECG's on subjects previously discussed will be included. The following week, a detailed interpretation of the "unknown" tracings will be enclosed in the new lesson. Clinical case histories will be available for correlation.

The advanced course is designed to meet the needs of the physician who has already gained facility in ECG interpretation but desires prolonged weekly supervised practice to maintain and improve his skill. Each week for a year, six unknown tracings with the clinical histories will be presented for study. A detailed description, interpretation and explanation will be sent the following week.

Inquiries should be addressed to Postgraduate Division, University of Southern California, School of Medicine, Los Angeles 33, California.

Harvey Tercentenary Exhibit

In connection with the tercentenary commemoration (1957) of William Harvey, the National Heart Institute and the National Library of medicine have prepared an exhibit "William Harvey and the Circulation of the Blood."

Catalog of the Exhibit is obtainable from the Heart Information Center, National Heart Institute, National Institute of Health, Bethesda 14, Md.

Dr. Schmidt Succeeds Dr. Wiggers

Dr. Carl F. Schmidt, Professor of Pharmacology at the University of Pennsylvania School of Medicine, Philadelphia, has succeeded Dr. Carl J. Wiggers as Editor of *Circulation Research.* Dr. Schmidt is a former Vice-President of the College and Dr. Wiggers is an Honorary Fellow. We congratulate Dr. Schmidt and wish him success. We know that he will maintain the high standards set by Dr. Wiggers.